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(54) **ARYL SUBSTITUTED CARBOXAMIDE DERIVATIVES AS CALCIUM OR SODIUM CHANNEL BLOCKERS**

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See application file for complete search history.

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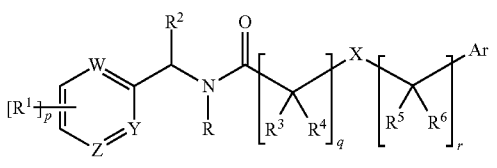
(57) **ABSTRACT**

The present invention relates to aryl substituted carboxamide derivatives of formula (I) or a pharmaceutically acceptable salt thereof, which have blocking activities of T-type calcium channels or voltage gated sodium channels as the tetrodotoxin-sensitive (TTX-S) blockers such as $Na_{V1.3}$ and $Na_{V1.7}$, and which are useful in the treatment or prevention of disorders and diseases in which T-type calcium channels or voltage gated sodium channels are involved. The invention also relates to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which T-type calcium channels or voltage gated sodium channels are involved.

(I)



5 Claims, No Drawings

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ARYL SUBSTITUTED CARBOXAMIDE DERIVATIVES AS CALCIUM OR SODIUM CHANNEL BLOCKERS

This application is a U.S. national stage of International Application No. PCT/JP2010/003649 filed May 31, 2010, which claims the benefit of U.S. provisional application Ser. Nos. 61/213,324 filed May 29, 2009; 61/272,581 filed Oct. 7, 2009 and 61/282,534 filed Feb. 26, 2010.

TECHNICAL FIELD

The present invention relates to aryl substituted carboxamide derivatives which have blocking activities of T-type calcium channels or voltage gated sodium channels as the tetrodotoxin-sensitive (TTX-S) blockers such as $Na_{V1.3}$ and $Na_{V1.7}$, and which are useful in the treatment or prevention of disorders and diseases in which T-type calcium channels or voltage gated sodium channels are involved. The invention also relates to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which T-type calcium channels or voltage gated sodium channels are involved.

BACKGROUND ART

Plasma membrane calcium channels are members of a diverse superfamily of voltage gated channel proteins. Calcium channels are membrane-spanning, multi-subunit proteins that allow controlled entry of Ca^{2+} ions into cells from the extracellular fluid. Excitable cells throughout the animal kingdom, and at least some bacterial, fungal and plant cells, possess one or more types of calcium channel. Nearly all "excitable" cells in animals, such as neurons of the central nervous system (CNS), peripheral nerve cells and muscle cells, including those of skeletal muscles, cardiac muscles, and venous and arterial smooth muscles, have voltage dependent calcium channels.

Multiple types of calcium channels have been identified in mammalian cells from various tissues, including skeletal muscle, cardiac muscle, lung, smooth muscle and brain. A major type of this family is the L-type calcium channels, whose function is inhibited by the familiar classes of calcium channel blockers (dihydropyridines such as nifedipine, phenylalkylamines such as verapamil, and benzothiazepines such as diltiazem). Additional classes of plasma membrane calcium channels are referred to as T-type, N-type, P-type, Q-type and R-type.

The "T-type" (or "low voltage-activated") calcium channels are so named because their openings are of briefer duration (T=transient) than the longer (L=long-lasting) openings of the L-type calcium channels. The L, N, P and Q-type channels activate at more positive potentials (high voltage activated) and display diverse kinetics and voltage-dependent properties.

T-type calcium channels have been implicated in pathologies related to various diseases and disorders, including epilepsy, essential tremor, pain, neuropathic pain, schizophrenia, Parkinson's disease, depression, anxiety, sleep disorders, sleep disturbances, insomnia, psychosis, cardiacarrhythmia, hypertension, cancer, diabetes, infertility and sexual dysfunction (J Neuroscience, 14, 5485 (1994); Drugs Future 30(6), 573-580 (2005); EMBO J, 24, 315-324 (2005); Drug Discovery Today, 11, 5/6,245-253 (2006); Neuropharmacology 53, 308-317 (2007) and J. Biol. Chem., 283(15), 10162-10173 (2008)).

On the other hand, blockers of voltage gated sodium channels as the TTX-S channels also relates to a number of therapeutic applications.

The rat $Na_{V1.3}$ channel and the human $Na_{V1.3}$ channel have been cloned in 1988 and 1998/2000 respectively (FEBS Lett. 228 (1), 187-194, 1988; J. Mol. Neurosci., 10 (1), 67-70, 1998; Eur. J. Neurosci. 12 (12), 4281-4289, 2000). The $Na_{V1.3}$ channel was formerly known as brain type III sodium channel. $Na_{V1.3}$ is present at relatively high levels in the nervous system of rat embryos but is barely detectable in adult rats. $Na_{V1.3}$ is up-regulated following axotomy in the Spinal Nerve Ligation (SNL), Chronic Constriction Injury (CCI), and diabetic neuropathy models (J Neurophysiol 82, 2776-2785, 1999. J. A. Black et al; Ann Neurol 52, 786-792, 2002. M. J. Cranner et al; Pain 83, 591-600, 1999. S. Dib-Hajj et al; J Biol Chem 279, 29341-29350, 2004. S. Hong et al; Mol Brain Res 95, 153-161, 2001. C. H. Kim et al.) The up-regulation of $Na_{V1.3}$ channel contributes to rapidly repriming sodium current in small dorsal root ganglion (DRG) neurons (J Neurophysiol 82, 2776-2785, 1999. J. A. Black et al.). These observations suggest that $Na_{V1.3}$ may make a key contribution to neuronal hyperexcitability.

In order to validate the contribution of $Na_{V1.3}$ sodium channel in the pain states, specific antisense oligonucleotides (ASO) were used in animal pain models. $Na_{V1.3}$ sodium channel ASO treatment significantly attenuated pain-related behaviors after CCI operation (J. Neurosci. 24, 4832-4839, 2004, Haim, B. C. et al.). These finding suggest that $Na_{V1.3}$ sodium channel antagonist is useful to treat neuropathic pain conditions.

The $Na_{V1.7}$ channel appears to be the best 'validated' pain target. The most exciting findings with respect to $Na_{V1.7}$ have come from human genetic studies. Cox et al. (Nature 444, 894-898, 2006) discovered SCN9A mutations that cause a loss of $Na_{V1.7}$ function in three families from Pakistan. Their observations link loss of $Na_{V1.7}$ function with a congenital inability to experience pain, adding to the evidence indicating $Na_{V1.7}$ channel as an essential participant in human nociception.

By contrast, Gain-of-function mutations have also been described that lead to enhanced pain, for example, Primary Erythermalgia in one case and Paroxysmal Extreme Pain Disorder in another. These gain-of-function mutations in patients led to different types of gating changes in $Na_{V1.7}$ sodium currents and, interestingly, different degrees of effectiveness of specific sodium channel blocking drugs. The implication from these findings is that a selective $Na_{V1.7}$ blocker may be an effective treatment for pain in man.

A local anaesthetic lidocaine and a volatile anaesthetic halothane are known to act on both TTX-R and TTX-S sodium channels with poor selectivity and low potency (IC_{50} values range from 50 mM to 10 mM). These anaesthetics at high systemic concentrations could cause devastating side effects, e.g., paralysis and cardiacarrest. However, systemic administration of lidocaine at low concentrations is effective to treat chronic pain (Trends in Pharm. Sci 22, 27-31, 2001, Baker, M. D. et al.). In rats, application of a very low dose of TTX to the DRG of the injured segment of the L5 spinal nerve significantly reduces mechanical allodynic behavior (Brain Res 871, 98-103, 2000, Lyu, Y. S. et al.). This suggests that TTX-S subtypes of sodium channels play an important role in maintaining allodynic behaviors in an animal model of neuropathic pain.

The $Na_{V1.5}$ channel is also a member of TTX-resistant sodium channels. The $Na_{V1.5}$ channel is almost exclusively expressed in cardiac tissue and has been shown to underlie a variety of cardiacarrhythmias and conduction disorders.

In particular, the aryl substituted carboxamide derivatives of the present invention are selective for the TTX-S channels over the $Na_{V1.5}$ channel, leading to improvements in the side-effect profile.

The aryl substituted carboxamide derivatives are therefore useful for the treatment of a wide range of disorders, particularly pain, acute pain, chronic pain, neuropathic pain, inflammatory pain, visceral pain, nociceptive pain including post-surgical pain, and mixed pain types involving the viscera, gastrointestinal tract, cranial structures, musculoskeletal system, spine, urogenital system, cardiovascular system and CNS, including cancer pain, back and orofacial pain.

Other conditions that may be treated with the picolinamide derivatives of the present invention include multiple sclerosis, neurodegenerative disorders, irritable bowel syndrome, osteoarthritis, rheumatoid arthritis, neuropathological disorders, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis, pancreatitis, migraine, cluster and tension headaches, diabetic neuropathy, peripheral neuropathic pain, sciatica, fibromyalgia Crohn's disease, epilepsy or epileptic conditions, bipolar depression, tachyarrhythmias, mood disorder, bipolar disorder, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, incontinence, visceral pain, trigeminal neuralgia, herpetic neuralgia, general neuralgia, postherpetic neuralgia, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, breakthrough pain, postsurgical pain, stroke, cancer pain, seizure disorder and causalgia.

WO2007120729, WO2009054982, WO2009054983, and WO2009054984 disclose a series of heterocycle amide compounds which are blockers of T-type calcium channels.

The compounds of the present invention, however, differ structurally from known compounds in the above cited arts by the presence of unique spacer between carbony group and terminal aryl group. Namely, disclosed compounds of the prior arts are introducing only one carbon atom as a spacer between carbonyl group and heteroaryl, whereas the compounds of the present invention are characterized by introducing different unique spacers between carbony group and terminal aryl group.

WO 2003037274 discloses pyrazole derivatives as sodium channel blockers. Then WO2002091830 disclosed pyridinyl fused bicyclic amides as fungicides.

The novel compounds with trifluoroethoxy or methoxy on the pyridine ring or pyrazine ring; and alkyl side chain; are useful for the treatment of a condition or disorder in which voltage gated sodium channels are involved.

On the contrary, cyclopropane carboxamide besides trifluoroethoxy or methoxy on the pyridine ring or pyrazine ring is important for the treatment of a condition or disorder in which T-type calcium channels are involved. The compounds have advantage over the compounds disclosed in WO2007120729, WO2009054982, WO2009054983, and WO2009054984 in terms of metabolism.

The above cited arts, however, have never disclosed the voltage gated sodium channels. Therefore aryl substituted carboxamide derivatives of this invention provide the first knowledge of blocking not only the T-type calcium channels but also voltage gated sodium channels.

It is an objective of the invention to provide new T-type calcium channel blockers or TTX-S blockers that are good drug candidates. Preferred compounds should bind potently to the TTX-S ($Na_{V1.3}$ and $Na_{V1.7}$) channels whilst showing little affinity for other sodium channels, particularly the $Na_{V1.5}$ channel. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favorable pharmacokinetic properties. For example, the compounds of this invention have excellent metabolic properties comparing with the compounds disclosed in WO 2007120729, WO 2009054982, WO 2009054983, and WO 2009054984. They should be non-toxic and demonstrate few side-effects. Furthermore, the ideal drug candidate will exist in a physical form that is stable, non-hygroscopic and easily formulated.

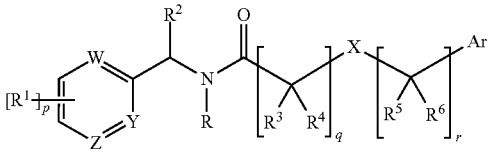
SUMMARY OF INVENTION

The present invention is directed to aryl substituted carboxamide derivatives which are blockers of T-type calcium channels or voltage gated sodium channels, and which are useful in the treatment or prevention of neurological and psychiatric disorders and diseases in which T-type calcium channels or voltage gated sodium channels are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which T-type calcium channels or voltage gated sodium channels are involved. It is needless to say that T-type calcium channels or voltage gated sodium channels does cover T-type calcium channels and voltage gated sodium channels.

DESCRIPTION OF EMBODIMENTS

The present invention provides a use of a compound of the following formula (I) for the manufacture of a medicament for the treatment of a condition or disorder in which T-type calcium channels or voltage gated sodium channels are involved:

[Chem. 1]



wherein:

R is hydrogen or C_{1-6} alkyl which may be substituted with one or more substituents independently selected from R^7;

R^1 is independently selected from the group consisting of; (1) hydrogen, (2) halogen, (3) hydroxyl, (4) $—O_n—C_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from R^7, (5) $—O_n—C_{3-6}$ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from R^7, (6) C_{2-4} alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents independently selected from R^7, (7) $—O_n$-phenyl or $—O_n$-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents independently selected from R^7, (8) $—O_n$-heterocyclic group, where the heterocyclic group is unsubstituted or substituted with one or more substituents independently selected from R^7, (9) $—(C═O)—NR^9R^{10}$, (10) $—NR^9R^{10}$, (11) $—S(O)_2—NR^9R^{10}$, (12) $—NR^9—S(O)_2R^{10}$, (13) $—S(O)_t—R^9$, where t is 0, 1 or 2, (14) $—NR^9(C═O)R^{10}$, (15) —CN, and (16) $—NO_2$;

wherein n is 0 or 1, when n is 0, a chemical bond is present in the place of O_n;

p is 1, 2, 3, or 4; when p is two or more than two, R^1 may be same or different;

R^2 is selected from the group consisting of:

(1) hydrogen, (2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (3) C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (4) C_{2-6} alkenyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (5) C_{2-6} alkynyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (6) phenyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (7) —(C═O)—NR^9R^{10}, and (8) —(C═O)—O—C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7;

or R^2 form a 5 to 7 membered ring with R^1 which may contain nitrogen atom, oxygen atom, sulfur atom or double bond, wherein the 5 to 7 membered ring is optionally substituted with 1 to 6 substituents independently selected from the group consisting of: (1) hydrogen, (2) hydroxyl, (3) halogen, (4) C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (5) C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (6) —O—C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, and (7) —O—C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7;

X is a chemical bond, —C≡C—, -cycloalkylene-, -cycloalkylene-C_{1-4}-alkylene-O—, oxygen atom, sulfur atom, or nitrogen atom; when X is —C≡C—, -cycloalkylene-, -cycloalkylene-C_{1-4}-alkylene-O—, or nitrogen atom, said substituent X may have a substituent independently selected from the definitions of R^9 and R^{10};

W, Y and Z are independently selected from nitrogen atom and carbon atom, which are independently optionally substituted with R^1;

at least one of W, Y and Z is nitrogen and W, Y and Z are not carbon at the same time;

R^3, R^4, R^5 and R^6 are independently selected from the group consisting of:

(1) hydrogen, (2) hydroxyl, (3) halogen, (4) C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (5) C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (6) —O—C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, (7) —O—C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^7, and (8) —NR^7R^8;

or R^3 and R^4 and the carbon atom to which they are attached form an oxo group;

or R^3 and R^4 and the carbon atom to which they are attached form a C_{3-6} cycloalkyl ring, which is unsubstituted or substituted with R^7;

or R^5 and R^6 and the carbon atom to which they are attached form an oxo group;

or R^5 and R^6 and the carbon atom to which they are attached form a C_{3-6} cycloalkyl ring, which is unsubstituted or substituted with R^7;

q is 0, 1, 2, 3, or 4; when q is one or more than one, R^3 and R^4 may be same or different;

r is 0, 1, 2, 3, or 4; when r is one or more than one, R^5 and R^6 may be same or different;

when (i) q is 1 and r is 0 or (ii) q is 0 and r is 1, X is not a chemical bond;

R^7 is selected from the group consisting of:

(1) hydrogen, (2) halogen, (3) hydroxyl, (4) —$(C═O)_m$—O_1—C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from R^8, (5) —O_1—(C_{1-3})perfluoroalkyl, (6) —$(C═O)_m$—O_1—C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from R^8, (7) —$(C═O)_m$—C_{2-4}alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents independently selected from R^8, (8) —$(C═O)_m$—O_1-phenyl or —$(C═O)_m$—O_1-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents independently selected from R^8, (9) —$(C═O)_m$—O_1-heterocyclic group, where the heterocyclic group is unsubstituted or substituted with one or more substituents independently selected from R^8, (10) —(C═O)—NR^9R^{10}, (11) —NR^9R^{10}, (12) —$S(O)_2$—NR^9R^{10}, (13) —$S(O)_t$—R^9, where t is 0, 1 or 2, (14) —CO_2H, (15) —CN, and (16) —NO_2;

wherein 1 is 0 or 1 and m is 0 or 1; when 1 is 0 or m is 0, a chemical bond is present in the place of $(C═O)_m$ or O_1, and when 1 is 0 and m is 0, a chemical bond is present in the place of $(C═O)_m$—O_1;

R^8 is independently selected from the group consisting of: (1) hydrogen, (2) hydroxyl, (3) halogen, (4) C_{1-6} alkyl, (5) —C_{3-6} cycloalkyl, (6) —O—C_{1-6} alkyl, (7) —O(C═O)—C_{1-6} alkyl, (8) —NH—C_{1-6} alkyl, (9) phenyl, (10) heterocyclic group, and (11) —CN;

R^9 and R^{10} are independently hydrogen or C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl; or R^9 form a 4 to 7 membered ring with R^{10} which may contain nitrogen atom, oxygen atom, sulfur atom or double bond, wherein the 4 to 7 membered ring is optionally substituted with 1 to 6 substituents independently selected from the group consisting of: (1) hydrogen, (2) hydroxyl, (3) halogen, (4) C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^8, (5) C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^8, (6) —O—C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^8, and (7) —O—C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^8;

Ar is aryl which is optionally substituted with 1 to 5 substituents independently selected from the group consisting of:

(1) halogen, (2) hydroxyl, (3) —O_n-phenyl or —O_n-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents independently selected from R^7, (4) —O_n-heterocyclic group, where the heterocyclic group is unsubstituted or substituted with one or more substituents independently selected from R^7, (5) —O_n—C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from R^7, (6) —O_n—C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from R^7, (7) —C_{2-4} alkenyl, where the alkenyl is unsubstituted or substituted with one or more substituents independently selected from R^7, (8) —(C═O)—NR^9R^{10}, (9) —NR^9R^{10}, (10) —$S(O)_2$—NR^9R^{10}, (11) —NR^9—$S(O)_2R^{10}$, (12) —$S(O)_t$—R^9, where t is 0, 1 or 2, (13) —NR^9(C═O)R^{10}, (14) —CN, and (15) —NO_2;

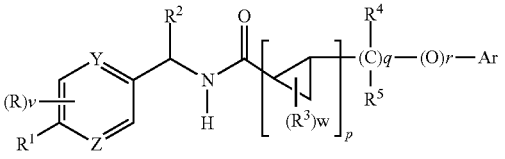
wherein n is 0 or 1, when n is 0, a chemical bond is present in the place of O_n;

or a pharmaceutically acceptable salt thereof.

The present invention provides the compounds of the formula (II)

[Chem. 2]

(II)



wherein

R is halogen, or C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl;

v is 0, 1, 2, or 3; when v is two or more than two, R may be same or different;

R^1 is —OCH_2CF_3 or —OCH_3;

R^2 is C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl;

R^3 is independently selected from the group consisting of:

(1) halogen, (2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^6, (3) C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^6, (4) —O—C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^6, (5) —O—C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^6, and (6) —NR^7R^8—;

Preferable R^3 is independently selected from the group consisting of:

(1) halogen, (2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from halogen;

w is 0, 1, 2, 3 or 4; when w is two or more than two, R^3 may be same or different;

R^4 and R^5 are independently hydrogen, halogen, or C_{1-6} alkyl which is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl;

Preferable R^4 and R^5 are independently hydrogen, halogen, or C_{1-6} alkyl which is unsubstituted or substituted with one or more substituents independently selected from halogen;

R^6 is independently selected from the group consisting of:

(1) hydrogen, (2) hydroxyl, (3) halogen, (4) —O_1R^7, (5) —CN, (6) —(C═O)—NR^7R^8, (7) —NR^7R^8, (8) —$S(O)_2$—NR^7R^8, (9) —$S(O)_t$—R^7, where t is 0, 1 or 2, (10) —CN, and (11) —NO_2;

wherein 1 is 0 or 1; when 1 is 0, a chemical bond is present in the place of O_1;

R^7 and R^8 are independently hydrogen, C_{1-6} alkyl, or C_{3-8} cycloalkyl, which are un-substituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl; or R^7 form a 4 to 7 membered ring with R^8 which may contain nitrogen atom, or oxygen atom, wherein the 4 to 7 membered ring is optionally substituted with 1 to 6 substituents independently selected from the group consisting of: (1) hydrogen, (2) hydroxyl, (3) halogen, (4) C_{1-6} alkyl, and (5) —O—C_{1-6} alkyl;

p, q, and r are independently 0 or 1; when p is 0, both q and r are 1 or both q and r are 0.

Y and Z are independently selected from nitrogen atom and carbon atom; Y and Z are not carbon atom at the same time;

when p is 0, Ar is selected from the group consisting of phenyl, indolyl and quinolinyl; wherein Ar is optionally substituted with 1 to 5 substituents independently selected from the group consisting of:

(1) halogen, (2) hydroxyl, (3) —O-phenyl or —O-napthyl, where the phenyl or napthyl is unsubstituted or substituted with one or more substituents independently selected from R^6, (4) —O_n-heterocyclic group, where the heterocyclic group is unsubstituted or substituted with one or more substituents independently selected from R^6, (5) —O_n—C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from R^6, (6) —O_n—C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from R^6, (7) —NR^7R^8, (8) —$S(O)_2$—NR^7R^8, (9) —$S(O)_t$—R^7, where t is 0, 1 or 2, (10) —$NR^7SO_2R^8$, (11) —(C═O)—NR^7R^8, (12) —NR^7(C═O)R^8, (13) —CN, and (14) —NO_2;

wherein preferable Ar is optionally substituted with 1 to 5 substituents independently selected from the group consisting of:

(1) halogen, (2) hydroxyl, (3) —O-phenyl, where the phenyl is unsubstituted or substituted with one or more substituents independently selected from halogen, methyl, trifluoromethyl, and trifluoromethoxy, (4) —O_n-heterocyclic group, where the heterocyclic group is unsubstituted or substituted with one or more substituents independently selected from halogen, methyl, trifluoromethyl, and trifluoromethoxy, (5) —O n-C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, (6) —O_n—C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, and (7) —CN;

wherein n is 0 or 1, when n is 0, a chemical bond is present in the place of O_n;

when p is 1, Ar is aryl which is optionally substituted with 1 to 5 substituents independently selected from the group consisting of:

(1) halogen, (2) hydroxyl, (3) —O_n-heterocyclic group, where the heterocyclic group is unsubstituted or substituted with one or more substituents independently selected from R^6, (4) —O_n—C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from R^6, (5) —O_n—C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from R^6, (6) —NR^7R^8, (7) —$S(O)_2$—NR^7R^8, (8) —$S(O)_t$—R^7, where t is 0, 1 or 2, (9) —$NR^7SO_2R^8$, (10) —(C═O)—NR^7R^8, (11) —NR^7(C═O)R^8, (12) —CN, and (13) —NO_2;

when p is 1, preferable Ar is aryl which is optionally substituted with 1 to 5 substituents independently selected from the group consisting of:

(1) halogen, (2) hydroxyl, (3) —O_n—C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, (4) —O_n—C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, and (5) —CN;

wherein n is 0 or 1, when n is 0, a chemical bond is present in the place of O_n;

or a pharmaceutically acceptable salt thereof.

Suitable compounds of the invention are:

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide;

(R)-3,5-dichloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl) quinoline-2-carboxamide;

(1R,2R)-2-methyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxamide;

(R)-4-tert-butyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(R)-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide;

(R)-2-(p-tolyloxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-4-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;

(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-1H-indole-2-carboxamide;

(R)-2-(2,4-dichlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-2-(4-bromophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)acetamide;

(R)-3-(3-fluorophenyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide;

(R)-3-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)benzofuran-2-carboxamide;

(R)-5-tert-butyl-2-methyl-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)furan-3-carboxamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(trifluoromethyl)benzamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4-(trifluoromethyl)benzamide;

(R)-5-phenyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-2-(trifluoromethyl)furan-3-carboxamide;

(R)-3-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-5-(trifluoromethyl)benzamide;

(R)-3-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-4-(trifluoromethyl)benzamide;

(R)-4-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-3-(trifluoromethyl)benzamide;

(R)-2-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-6-(trifluoromethyl)-2H-indazole-3-carboxamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethyl)picolinamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide;

(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-1H-indole-3-carboxamide;

(R)-3-(1H-indol-1-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide;

(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-5-(trifluoromethyl)-1H-indole-2-carboxamide;

(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-5-fluoro-1H-indole-2-carboxamide;

(R,E)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-3-(4-(trifluoromethyl)phenyl)acrylamide

(R,E)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-3-(4-(trifluoromethyl)phenyl)acrylamide

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)thiazole-4-carboxamide;

(R)-3-(6-fluoro-1H-indol-1-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide;

(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-3-(6-fluoro-1H-indol-1-yl)propanamide;

(R)-N-(1-(5-(2-fluorobenzyloxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide;

(R)-5-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)picolinamide;

(R)-N-(1-(5-(pyridin-2-ylmethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide;

N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxamide;

(R,E)-3-(1H-indol-3-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acrylamide (1R,2R)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxamide;

(R)-N-(1-(5-((1-methylcyclopropyl)methoxy)pyridin-2-yl) ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide;

trans-2-(7-fluoro-1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(R)-3-chloro-4-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(R)-4-tert-butyl-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)benzamide;

(R)-3-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)benzamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)quinoxaline-2-carboxamide;

(R)-4-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)quinoline-2-carboxamide;

(R)-5-isobutyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)isoxazole-3-carboxamide;

(R)-3-(2-methylthiazol-4-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzo[b]thiophene-2-carboxamide;

(R)-3-(benzyloxy)-4-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(R)-3-phenoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)benzamide;

(1S*,2S*)-2-(1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(R)-5-chloro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide;

(R)-5-methoxy-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)-1H-indole-3-carboxamide;

(R)-1,6-dimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide;

(R)-6-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide;

(R)-5-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-1H-indole-3-carboxamide;

(R)-5-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-1H-indole-3-carboxamide;

(R)-5-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-1H-indole-3-carboxamide;

(R)-6-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-1H-indole-3-carboxamide;

trans-2-(1H-indol-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy) pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(R)-1,5-dimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;

(R)-5-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;

(R)-5-chloro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;

(R)-6-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4-(trifluoromethoxy)benzamide;

(R)-5-phenyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)isoxazole-3-carboxamide;

(R)-5-bromo-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;

(R)-6-chloro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;

(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethoxy)-1H-indole-2-carboxamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(trifluoromethoxy)benzamide;

trans-2-(quinolin-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(isoquinolin-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-((4-chlorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(2-fluoro-5-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-((1H-indol-1-yl)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(R)-6-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-1H-indole-2-carboxamide;

trans-2-(2,5-difluorophenyl)-N-((R)-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(2,5-difluorophenyl)cyclopropanecarboxamide;

trans-2-(2,5-difluorophenyl)-N-((R)-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(1H-indol-4-yl)cyclopropanecarboxamide;

trans-2-(4-methoxy-3-methylphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(1H-indol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

trans-2-(5-fluoro-1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-3-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

trans-2-(1H-indol-4-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(8-chloroquinolin-2-yl)-N-((R)-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(R)-5-methoxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-1H-indole-2-carboxamide;

(R)-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-4-(trifluoromethoxy)benzamide;

(R)-3-phenoxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)benzamide;

(R)-6-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)quinoline-2-carboxamide;

(1S*,2S*)-2-(1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(1H-indol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(1-methyl-1H-indazol-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(4-(benzyloxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(R,E)-3-(quinolin-2-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acrylamide;

(1S*,2S*)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(3,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(3-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(4-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(2-chloro-4-fluorophenyl)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(2-fluoro-4-methoxyphenyl)cyclopropanecarboxamide;

(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl)cyclopropanecarboxamide;

(1S*,2S*)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl)cyclopropanecarboxamide;

(1R*,2R*)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(1H-indol-4-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-phenyl-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-phenyl-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-((3-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-((3-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-((4-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-((4-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-((3-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-((3-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-((4-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-((4-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(4-((3-methyloxetan-3-yl)methoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(1H-indol-7-yl)cyclopropanecarboxamide;

(1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

4-(benzyloxy)-3-methoxy-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)benzamide;

2-(4-(trifluoromethyl)phenoxy)-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;

(R)-N-(1-(6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide;

(R)-5-fluoro-N-(1-(6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;

(S)-4-isopropyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(S)-2-(4-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(S)-4-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(1S*,2S*)-2-(4-(benzyloxy)phenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(4-(benzyloxy)phenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(2-fluoro-4-methoxyphenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(2-fluoro-4-methoxyphenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(2-chloro-4-fluorophenyl)-N-((S)-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(2-chloro-4-fluorophenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-phenyl-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-phenyl-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

tert-butyl
((R)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethoxy)phenyl)propan-2-yl)carbamate;

tert-butyl
((R)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethyl)phenyl)propan-2-yl)carbamate;

(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-3-phenoxybenzamide;

(R)-2-hydroxy-4-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)butanamide;

tert-butyl
((S)-1-(4-chlorophenyl)-3-oxo-3-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propyl)carbamate;

tert-butyl
((R)-1-(4-chlorophenyl)-3-oxo-3-4(R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propyl)carbamate;

tert-butyl
((R)-3-(4-chlorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate;

tert-butyl
((S)-3-(2-chlorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate;

tert-butyl
((S)-3-(2-fluorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate;

(R)-2-(2-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-2-(3-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-2-(2-chlorophenoxy)-2-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide;

(R)-2-(2,3-dichlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-2-(o-tolyloxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-2-(m-tolyloxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-2-(2,4-dimethylphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-2-(2-chloro-6-methylphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;

(R)-2-(4-(tert-butyl)phenoxy)-N-(1-(5-methoxypyridin-2-yl)ethyl)acetamide;

(R)-2-amino-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(2-(trifluoromethyl)phenyl)propanamide;

isobutyl
((R)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethyl)phenyl)propan-2-yl)carbamate;

ethyl
((R)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethyl)phenyl)propan-2-yl)carbamate;

N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-3-(trifluoromethoxy)benzamide;

4-(2,2,2-trifluoroethoxy)-N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)benzamide;

6-fluoro-1-methyl-N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-1H-indole-2-carboxamide;

3-(2,2,2-trifluoroethoxy)-N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)benzamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)phenoxy)acetamide;

(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(2-(trifluoromethoxy)phenoxy)acetamide;

(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)phenoxy)acetamide;

(R)-3-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;

(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)thiazole-4-carboxamide;
(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-1-methyl-5-(trifluoromethoxy)-1H-indole-2-carboxamide;
(R)-2-(4-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)acetamide;
(R)-5-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)picolinamide;
(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-3-(trifluoromethoxy)benzamide;
(R)-4-fluoro-3-phenoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
4-(tert-butyl)-N-((6-methoxypyridin-3-yl)methyl)benzamide;
N-((6-methoxypyridin-3-yl)methyl)-2-(4-(trifluoromethyl)phenoxy)acetamide;
4-(tert-butyl)-N-((5-methoxypyridin-2-yl)methyl)benzamide;
(S)-4-(tert-butyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
(S)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(trifluoromethoxy)benzamide;
(S)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4-(trifluoromethoxy)benzamide;
(S)-3-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-4-(trifluoromethoxy)benzamide;
(R)-4-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)benzamide;
(R)-3-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)benzamide;
4-(tert-butyl)-N-(5-(trifluoromethyl)pyridin-2-yl)methyl)benzamide;
3-(trifluoromethoxy)-N-((5-(trifluoromethyl)pyridin-2-yl)methyl)benzamide;
4-(trifluoromethoxy)-N-((5-(trifluoromethyl)pyridin-2-yl)methyl)benzamide;
4-(2,2,2-trifluoroethoxy)-N-((5-(trifluoromethyl)pyridin-2-yl)methyl)benzamide;
3-(2,2,2-trifluoroethoxy)-N-((5-(trifluoromethyl)pyridin-2-yl)methyl)benzamide;
4-(tert-butyl)-N-((6-(piperidin-1-yl)pyridin-3-yl)methyl)benzamide;
N-((6-(piperidin-1-yl)pyridin-3-yl)methyl)-3-(trifluoromethoxy)benzamide;
N-((6-(piperidin-1-yl)pyridin-3-yl)methyl)-4-(2,2,2-trifluoroethoxy)benzamide;
4-(tert-butyl)-N-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)benzamide;
N-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-3-(trifluoromethoxy)benzamide;
N-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-4-(2,2,2-trifluoroethoxy)benzamide;
4-(tert-butyl)-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)benzamide;
3-(trifluoromethoxy)-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)benzamide;
4-(tert-butyl)-N-((6-(pyrrolidin-1-yl)pyridin-2-yl)methyl)benzamide;
N-((6-(pyrrolidin-1-yl)pyridin-2-yl)methyl)-3-(trifluoromethoxy)benzamide;
N-((6-(pyrrolidin-1-yl)pyridin-2-yl)methyl)-4-(2,2,2-trifluoroethoxy)benzamide;
(R)-4-chloro-2-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
(R)-4-(2-cyanopropan-2-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
(R)-3-chloro-4-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
(R)-6-methoxy-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide;
(R)-N-(1-(6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(trifluoromethoxy)benzamide;
(R)-N-(1-(6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4-(2,2,2-trifluoroethox y)benzamide;
(S)-2-(3-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide;
2-(3-chlorophenoxy)-N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)acetamide;
(R)-2-(3-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)acetamide;
(R)-4-ethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
(R)-3-fluoro-4-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
(R)-5-chloro-2-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide;
(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)quinoxaline-2-carboxamide;
(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-5-(trifluoromethyl)picolinamide;

and salts thereof.

Also, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, for the manufacture of a medicament for the treatment of a condition or disorder mediated by T-type calcium channels or voltage gated sodium channels; in particular, T-type calcium channels blocking activity or voltage gated sodium channels blocking activity. In order to use the compounds of formula (I) and pharmaceutically acceptable salts thereof in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

Preferably, the present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, for the manufacture of a medicament for the treatment of diseases selected from T-type calcium channels related diseases or voltage gated sodium channels related diseases.

Also, the present invention provides the use of a compound of the formula (I) or the pharmaceutically acceptable salt thereof, each as described herein, for the manufacture of a medicament for the treatment of a condition or disorder in which voltage gated sodium channels are involved, as described in formula (I) herein wherein when Y is nitrogen atom, and at the same time (i) q is 1 and r is 0 or (ii) q is 0 and r is 1, then X may be a chemical bond;

or as described in formula (I) herein wherein when Y is carbon atom, Z is nitrogen atom, W is nitrogen atom, and at the same time (i) q is 1 and r is 0 or (ii) q is 0 and r is 1, then X may be a chemical bond;

the definition of the other descriptors is the same as described herein.

Also, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, together with a pharmaceutically acceptable carrier for said compound.

Also, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, together with a pharmaceutically acceptable carrier for said compound and another pharmacologically active agent.

Also, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

Also, the present invention provides an intermediate in a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Further, the present invention provides a method of treatment of a condition or disorder mediated by T-type calcium channels activity or voltage gated sodium channels activity, in a mammalian subject, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

Examples of conditions or disorders mediated by T-type calcium channels activity or voltage gated sodium channels activity include, but are not limited to, T-type calcium channels related diseases or voltage gated sodium channels related diseases. The compounds of the present invention show the T-type calcium channels blocking activity or voltage gated sodium channels blocking activity. The compounds of the present invention may show less toxicity, good absorption, distribution, good solubility, less protein binding affinity other than T-type calcium channels or voltage gated sodium channels, less drug-drug interaction, good metabolic stability, reduced inhibitory activity at HERG channel, and reduced QT prolongation.

As appreciated by those of skill in the art, "halogen" or "halo" as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C_{1-6}, as in C_{1-6} alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{1-8} alkyl specifically includes methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, pentyl, and hexyl. Similarly, C_{2-6} alkenyl is defined to identify the group as having 2, 3, 4, 5 or 6 carbons which incorporates at least one double bond, which may be in a E- or a Z-arrangement. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents.

The term "alkenyl", as used herein, means a hydrocarbon radical having at least one double bond including, but not limited to, ethenyl, propenyl, 1-butenyl, 2-butenyl and the like.

The term "cycloalkyl", as used herein, means a mono- or bicyclic ring, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norboranyl, and adamantyl groups and the like.

The term "aryl", as used herein, means mono- or bi-carbocyclic or mono- or bi-heterocyclic ring which may contain 0-4 heteroatoms selected from O, N and S, but not limited to, phenyl, furyl, thienyl, oxazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrrolyl, thiophenyl, pyrazinyl, pyridazinyl, isooxazolyl, isothiazolyl, triazolyl, furazanyl, naphthyl, tetrahydronaphthyl, indanyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indolyl, isoindolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, imidazopyridinyl, pyrazolopyrimidinyl, quinolyl, isoquinolyl, cinnolinyl, naphthyridinyl, phthalazinyl, quinazolinyl, quinoxalinyl, triazolopyrimidinyl, and the said rings which are fully or partially saturated, such as pyridin-2-onyl, piperidinyl, pyrrolidinyl, tetrehydronaphthalenyl, and the like.

The term "heterocyclic group" as used herein includes both unsaturated and saturated heterocyclic moieties, wherein the unsaturated heterocyclic moieties (i.e. "heteroaryl") include benzoimidazolyl, benzimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and N-oxides thereof, and wherein the saturated heterocyclic moieties include azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl, thiomorpholinyl, and tetrahydrothienyl, and N-oxides thereof and S-oxides thereof.

The term "C_0", as used herein, means direct bond.

The term "protecting group", as used herein, means a hydroxy or amino protecting group which is selected from typical hydroxy or amino protecting groups described in Protective Groups in Organic Synthesis edited by T. W. Greene et al. (John Wiley & Sons, 1991);

The term "treating" and "treatment", as used herein, refers to curative, palliative and prophylactic treatment, including reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition.

As used herein, the article "a" or "an" refers to both the singular and plural form of the object to which it refers unless indicated otherwise.

Included within the scope of the "compounds of the invention" are all salts, solvates, hydrates, complexes, polymorphs, prodrugs, radiolabeled derivatives, stereoisomers and optical isomers of the compounds of formula (I).

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci, 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, formic, acetic, trifluoroacetic, propionic, fumaric, citric, tartaric, benzoic, ptoluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counter ion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The compounds of formula (I) and salts thereof may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This inven-

tion includes within its scope stoichiometric hydrates or solvates as well as compounds containing variable amounts of water and/or solvent.

Salts and solvates having non-pharmaceutically acceptable counter-ions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts.

The compounds of formula (I) may have polymorphs in crystalline form, which are within the scope of the present invention.

Additionally, the compounds of formula (I) may be administered as prodrugs. As used herein, a "prodrug" of a compound of formula (I) is a functional derivative of the compound which, upon administration to a patient, eventually liberates the compound of formula (I) in vivo. Administration of a compound of formula (I) as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of action of the compound in vivo; (b) modify the duration of action of the compound in vivo; (c) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome a side effect or other difficulty encountered with the compound. Typical functional derivatives used to prepare prodrugs include modifications of the compound that are chemically or enzymatically cleaved in vivo. Such modifications, which include the preparation of phosphates, amides, esters, thioesters, carbonates, and carbamates, are well known to those skilled in the art.

In certain of the compounds of formula (I), there may be some chiral carbon atoms. In such cases, compounds of formula (I) exist as stereoisomers. The invention extends to all optical isomers such as stereoisomeric forms of the compounds of formula (I) including enantiomers, diastereoisomers and mixtures thereof, such as racemates. The different stereoisomeric forms may be separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereoselective or asymmetric syntheses.

Certain of the compounds herein can exist in various tautomeric forms and it is to be understood that the invention encompasses all such tautomeric forms.

The invention also includes isotopically-labeled compounds, which are identical to those described herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as 3H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Compounds of the invention that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances, Isotopically labeled compounds of the invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, then substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The potencies and efficacies of the compounds of this invention for T-type calcium channels or voltage gated sodium channels can be determined by methodology well known in the art, including the "Ca^{2+} influx Assay", "Electrophysiology assay for T-type Ca^{2+}", "FRET Assay for Nays" and "Electrophysiology assay for Nays" as described herein. Compounds of formula (I) have demonstrated blocking activity at the T-type calcium channels, using the assays described herein.

The intrinsic T-type calcium channels blocking activity or voltage gated sodium channels blocking activity of a compound which may be used in the present invention may be determined by these assays. In particular, the compounds of the following examples had activity in blocking the T-type calcium channel or voltage gated sodium channels in the aforementioned assays, generally with an IC_{50} of less than about 10 microM, preferably less than about 1 microM, more preferably less than about 0.3 microM. Some of the compounds within the present invention had activity in blocking the T-type calcium channels or voltage gated sodium channels in the aforementioned assays with an IC_{50} of less than about 1 microM. Such a result is indicative of the intrinsic activity of the compounds in use as blockers of T-type calcium channels activity or voltage gated sodium channels activity.

With respect to other compounds disclosed in the art, the present compounds exhibit unexpected properties, such as with respect to duration of action and/or metabolism, such as increased metabolic stability, enhanced oral bioavailability or absorption, and/or decreased drug-drug interactions.

T-type calcium channels have been implicated in a wide range of biological functions. This has suggested a potential role for these receptors in a variety of disease processes in humans or other species. The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with calcium channels, including one or more of the following conditions or diseases: movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease, drug-induced parkinsonism, postencephalitic parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification), chronic fatigue syndrome, fatigue, including Parkinson's fatigue, multiple sclerosis fatigue, fatigue caused by a sleep disorder or a circadian rhythm disorder, medication-induced parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication induced postural tremor), Gilles de la Tourette's syndrome, seizure disorders, epilepsy, and dyskinesias [including tremor (such as rest tremor, essential tremor, postural tremor and intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), restless leg syndrome and dystonia (including generalised dystonia such as iodiopathic dystonia, drug-induced dystonia, symptomatic dystonia and paroxymal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, spasmodic dyspho-

nia, spasmodic torticollis, axial dystonia, dystonic writer's cramp and hemiplegic dystonia); heart disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, sexual and reproductive dysfunction, such as impaired fertility, infertility, diseases or disorders where abnormal oscillatory activity occurs in the brain, including depression, migraine, neuropathic pain, Parkinson's disease, psychosis and schizophrenia, as well as diseases or disorders where there is abnormal coupling of activity, particularly through the thalamus; enhancing cognitive function; enhancing memory; increasing memory retention; increasing trained performance; increasing immune response; increasing immune function; hot flashes; night sweats; extending life span; schizophrenia; muscle-related disorders that are controlled by the excitation/relaxation rhythms imposed by the neural system such as cardiac rhythm and other disorders of the cardiovascular system; conditions related to proliferation of cells such as vasodilation or vasorestriction and blood pressure; cancer; cardiacarrhythmia; hypertension; congestive heart failure; conditions of the genital/urinary system; disorders of sexual function and fertility; adequacy of renal function; responsivity to anesthetics; sleep disorders, sleep disturbances, including enhancing sleep quality, improving sleep quality, increasing sleep efficiency, augmenting sleep maintenance; increasing the value which is calculated from the time that a subject sleeps divided by the time that a subject is attempting to sleep; improving sleep initiation; decreasing sleep latency or onset (the time it takes to fall asleep); decreasing difficulties in falling asleep; increasing sleep continuity; decreasing the number of awakenings during sleep; decreasing intermittent wakings during sleep; decreasing nocturnal arousals; decreasing the time spent awake following the initial onset of sleep; increasing the total amount of sleep; reducing the fragmentation of sleep; altering the timing, frequency or duration of REM sleep bouts; altering the timing, frequency or duration of slow wave (i.e. stages 3 or 4) sleep bouts; increasing the amount and percentage of stage 2 sleep; promoting slow wave sleep; enhancing EEG-delta activity during sleep; increasing the amount of Delta sleep early in the sleep cycle, increasing REM sleep late in the sleep cycle; decreasing nocturnal arousals, especially early morning awakenings; increasing daytime alertness; reducing daytime drowsiness; treating or reducing excessive daytime sleepiness; increasing satisfaction with the intensity of sleep; increasing sleep maintenance; idiopathic insomnia; sleep problems; insomnia, hypersomnia, idiopathic hypersomnia, repeatability hypersomnia, intrinsic hypersomnia, narcolepsy, interrupted sleep, sleep apnea, obstructive sleep apnea, wakefulness, nocturnal myoclonus, REM sleep interruptions, jet-lag, shift workers' sleep disturbances, dyssomnias, night terror, insomnias associated with depression, emotional/mood disorders, Alzheimer's disease or cognitive impairment, as well as sleep walking and enuresis, and sleep disorders which accompany aging; Alzheimer's sundowning; conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules, conditions due to drugs which cause reductions in REM sleep as a side effect; fibromyalgia; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep; conditions which result from a diminished quality of sleep; mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder, mood disorders due to a general medical condition, and substance-induced mood disorders; anxiety disorders including acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, ischemic stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiacarrest, hypoglycemic neuronal damage; Huntington's Chorea; amyotrophic lateral sclerosis; multiple sclerosis; ocular damage; retinopathy; cognitive disorders; idiopathic and drug-induced Parkinson's disease; muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnestic disorders or age related cognitive decline; schizophrenia or psychosis including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced psychotic disorder; substance-related disorders and addictive behaviors (including substance-induced delirium, persisting dementia, persisting amnestic disorder, psychotic disorder or anxiety disorder; tolerance, dependence or withdrawal from substances including alcohol, amphetamines, *cannabis*, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); attention deficit/hyperactivity disorder (ADHD); conduct disorder; migraine (including migraine headache); urinary incontinence; overactive bladder (DAB); urge urinary incontinence (UUI); lower urinary tract symptoms (LUTS); substance tolerance, substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.); psychosis; schizophrenia; anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder); mood disorders (including depression, mania, bipolar disorders); trigeminal neuralgia; hearing loss; tinnitus; neuronal damage including ocular damage; retinopathy; macular degeneration of the eye; emesis; brain edema; pain, including acute pain, chronic pain, severe pain, intractable pain, inflammatory pain, chronic inflammatory pain, diabetic neuropathy, chronic neuropathic pain, post-traumatic pain, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, neuropathic pain, post-traumatic pain, trigeminal neuralgia, migraine and migraine headache.

Thus, in an embodiment the present invention provides methods for: treating, controlling, ameliorating or reducing the risk of epilepsy, including absence epilepsy; treating or controlling Parkinson's disease; treating essential tremor; treating or controlling pain, including neuropathic pain; enhancing the quality of sleep; augmenting sleep maintenance; increasing REM sleep; increasing slow wave sleep; decreasing fragmentation of sleep patterns; treating insomnia; enhancing cognition; increasing memory retention; treating or controlling depression; treating or controlling psychosis; or treating, controlling, ameliorating or reducing the risk

of schizophrenia, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of the present invention. The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

In a similar fashion to T-type calcium channels, tetrodotoxin-sensitive (TTX-S) voltage gated sodium channels such as $Na_{V1.3}$ and $Na_{V1.7}$ have been also implicated in a wide range of biological functions. This has suggested a potential role for these receptors in a variety of disease processes in humans or other species. The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with TTX-S sodium channels, including one or more of the following conditions or diseases: pain, acute pain, chronic pain, neuropathic pain, inflammatory pain, visceral pain, nociceptive pain, multiple sclerosis, neurodegenerative disorder, irritable bowel syndrome, osteoarthritis, rheumatoid arthritis, neuropathological disorders, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis, pancreatitis, migraine, cluster and tension headaches, diabetic neuropathy, peripheral neuropathic pain, sciatica, fibromyalgia Crohn's disease, epilepsy or epileptic conditions, bipolar depression, tachyarrhythmias, mood disorder, bipolar disorder, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, incontinence, visceral pain, trigeminal neuralgia, herpetic neuralgia, general neuralgia, postherpetic neuralgia, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, breakthrough pain, postsurgical pain, stroke, cancer pain, seizure disorder and causalgia.

The dosage of active ingredient in the compositions of this invention may be varied, however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The active ingredient may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy.

The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize.

Generally, dosage levels of between 0.0001 to 20 mg/kg of body weight daily are administered to the patient, e.g., humans and elderly humans, to obtain effective blockage of T-type calcium channel. The dosage range will generally be about 0.5 mg to 1.0 g per patient per day which may be administered in single or multiple doses.

In one embodiment, the dosage range will be about 0.5 mg to 500 mg per patient per day; in another embodiment about 0.5 mg to 200 mg per patient per day; in another embodiment about 1 mg to 100 mg per patient per day; and in another embodiment about 5 mg to 50 mg per patient per day; in yet another embodiment about 1 mg to 30 mg per patient per day. Pharmaceutical compositions of the present invention may be provided in a solid dosage formulation such as comprising about 0.5 mg to 500 mg active ingredient, or comprising about 1 mg to 250 mg active ingredient. The pharmaceutical composition may be provided in a solid dosage formulation comprising about 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg or 250 mg active ingredient. For oral administration, the compositions may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, such as 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, such as once or twice per day.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of the present invention or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present invention is envisioned. However, the combination therapy may also include therapies in which the compound of the present invention and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly.

Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the present invention. The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds.

Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is envisioned. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, including about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used. In such combinations the compound of the present invention and other active agents may be administered separately or in

conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

A T-type calcium channels blocker or voltage gated sodium channels blocker may be usefully combined with same or another pharmacologically active compound, or with two or more same or other pharmacologically active compounds, particularly in the treatment of inflammatory, pain and urological diseases or disorders. For example, a T-type calcium channels blocker or a voltage gated sodium channels blocker, particularly a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H1 antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex(registered trademark), a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (−)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone;
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiratmate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (alphaR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7-naphthyridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
- a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion(registered trademark) or sarizotan;
- a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteroid such as dexamethasone;
- a 5-HT receptor agonist or antagonist, particularly a 5-HT1B/1D agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a 5-HT2A receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
- a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;

Tramadol(registered trademark);

- a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1': 6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4] triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl) pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl) pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1alpha,3 alpha,5 alpha)(3-aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3 aminomethyl-5 methyl-heptanoic acid, (3S,5R)-3 amino-5 methyl-heptanoic acid, (3S,5R)-3 amino-5

methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy) proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R, 6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4] oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3 aminomethyl-5 methyl-octanoic acid, (3S,5R)-3 amino-5 methyl-nonanoic acid, (3S,5R)-3 amino-5 methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;

a cannabinoid;

metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;

a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;

a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (VivalanR), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;

a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;

an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl) amino]-5-heptenoic acid, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S, 4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl] thio]-5-thiazolebutanol, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino) ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;

an acetylcholinesterase inhibitor such as donepezil;

a prostaglandin E2 subtype 4 (EP4) antagonist such as N-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methyl-benzenesulfonamide or 4-[(1S)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl] benzoic acid;

a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,

a 5-lipoxygenase inhibitor, such as zileuton,

6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504);

a sodium channel blocker, such as lidocaine;

a calcium channel blocker, such as ziconotide, zonisamide, mibefradil;

a 5-HT3 antagonist, such as ondansetron;

and the pharmaceutically acceptable salts and solvates thereof.

Such combinations offer significant advantages, including synergistic activity, in therapy.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrate compositions are generally preferred. Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); tabletting lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants, buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound or pharmaceutically acceptable salt thereof.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of formula (I) or pharmaceutically acceptable salt thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of formula (I) or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under

vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of formula (I) or pharmaceutically acceptable salts thereof may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of formula (I) or pharmaceutically acceptable salts may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of formula (I) or pharmaceutically acceptable salts may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds formula (I) or pharmaceutically acceptable salts thereof may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) or pharmaceutically acceptable salts thereof may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose). The compounds of formula (I) and pharmaceutically acceptable salts thereof may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilized components.

General Synthesis

Throughout the instant application, the following abbreviations are used with the following meanings:

DIBAL-H Diisobutylaluminium hydride
DMF N,N-dimethylformamide
DMSO Dimethyl sulfoxide
EDC 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride
HOBT 1-Hydroxybenztriazole
HBTU 0-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium Hexafluorophosphate
HPLC High pressure liquid chromatography
TEMPO 2,2,6,6-Tetramethyl-1-piperidinyloxy
tR Retention time
MHz Megahertz
NMR Nuclear Magnetic Resonance
TFA Trifluoroacetic acid
THF Tetrahydrofuran
TLC Thin layer chromatography

The term of "base" is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and barium hydroxide; alkali metal hydrides, such as lithium hydride, sodium hydride, and potassium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, and potassium t-butoxide; alkali metal carbonates, such as lithium carbonate, sodium carbonate, potassium carbonate, and cesium carbonate; alkali metal hydrogencarbonates, such as lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; amines, such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), lutidine, and colidine; alkali metal amides, such as lithium amide, sodium amide, potassium amide, lithium diisopropyl amide, potassium diisopropyl amide, sodium diisopropyl amide, lithium bis(trimethylsilyl)amide and potassium bis(trimethylsilyl)amide. Of these, triethylamine, diisopropylethylamine, DBU, DBN, DABCO, pyridine, lutidine, colidine, sodium carbonate, sodium hydrogencarbonate, sodium hydroxide, potassium carbonate, potassium hydrogencarbonate, potassium hydroxide, barium hydroxide, and cesium carbonate are preferred.

The reactions are normally and preferably effected in the presence of inert solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include, but not limited to: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride, and dichloroethane; ethers, such as diethyl ether, diisopropyl ether, THF, and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as, DMF, N,N-dimethylacetamide, and hexamethylphosphoric triamide; amines, such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, N,N-dimethylaniline, and N,N-diethylaniline; alcohols, such as methanol, ethanol, propanol, isopropanol, and butanol; nitriles, such as acetonitrile and benzonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO) and sulfolane; ketones, such as acetone and diethylketone. Of these solvents, including but not limited to DMF, DMSO, THF, diethylether, diisopropylether, dimethoxyethane, acetonitrile, dichloromethane, dichloroethane and chloroform are preferred.

EXAMPLES

The invention is illustrated in the following non-limiting examples in which, unless stated otherwise: all reagents are commercially available, all operations were carried out at room or ambient temperature, that is, in the range of about 18-25° C.; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to about 60° C.; reactions were monitored by thin layer chromatography (tlc) and reaction times are given for illustration only; the structure and purity of all isolated compounds were assured by at least one of the following

techniques: tlc (Merck silica gel 60 F_{254} precoated TLC plates or Merck NH_2F_{254} precoated HPTLC plates), mass spectrometry or nuclear magnetic resonance (NMR). Yields are given for illustrative purposes only. Flash column chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM) or Fuji Silysia Chromatorex(registered trademark) DU3050 (Amino Type, 30-50 micrometer) or Biotage silica (32-63 micrometer, KP-Sil) or Biotage amino bounded silica (35-75 mlcrometer, KP-NH) or Hi-Flash Column™ (40 micrometer, Silica gel). Low-resolution mass spectral data (ESI) were obtained by the following apparatus and conditions: Apparatus; Waters Alliance HPLC system on ZQ or ZMD mass spectrometer and UV detector. NMR data was determined at 270 MHz (JEOL JNM-LA 270 spectrometer) or 300 MHz (JEOL JNM-LA300) using deuterated chloroform (99.8% D) or dimethylsulfoxide (99.9% D) as solvent unless indicated otherwise, relative to tetramethylsilane (TMS) as internal standard in parts per million (ppm); conventional abbreviations used are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, etc. Chemical symbols have their usual meanings;
μm (micrometer(s)), μL (microliter(s)), μg (microgram(s)), M (mol(s) per liter), L(liter(s)), mL (milliliter(s)), g (gram(s)), mg(milligram(s)), mol (moles), mmol (millimoles).

Purification Methods:

Achiral Reversed-phase HPLC:

Apparatus: Waters MS-trigger Autopurification™ System (2525 Binary pump module, 2767 Sample manager, 2996 PDA detector and Z02000 mass spectrometer)

Column: XBridge™ Prep C18 5 μm, 19×50 mm

Column temperature: ambient (room temperature)

Flow rate: 20 mL/min

Mobile phase A: Methanol or Acetonitrile/0.05% (v/v) formic acid aqueous solution

Mobile phase B: Methanol or Acetonitrile/0.05% (v/v) ammonia aqueous solution

Elution: Optimized gradient program with selected mobile phases

Run time: 7 min

MPLC:

Apparatus: Biotage SP System

Column: Hi-Flash™ Column Silica gel 40 μm, 60 Å

Column Temperature: room temperature

Solvents:

Less polar solvent: hexane

High polar solvent: ethyl acetate

Chiral Normal Phase HPLC:

Apparatus: Shimadzu Preparative-HPLC system

Column: DAICEL Chiralpak AD-H, 20×250 mm

DAICEL Chiralpak AS-H, 20×250 mm

DAICEL Chiralcel OJ-H, 20×250 mm

DAICEL Chiralcel OD-H, 20×250 mm

Column temperature: 40° C.

Solvents:

A1: n-Hexane

B1: Ethanol or 2-propanol

Elution: Optimized isocratic condition with the selected column and mobile phases

Purity Evaluation Method:

Method A:

Apparatus: Waters Acquity Ultra Performance LC on TUV Detector and ZQ mass spectrometer

Column: XTerra MS C18 3.5 μm, 2.1×30 mm

Column Temperature: 45° C.

Solvents:

A1: acetonitrile

B1: 5 mM ammonium acetate aqueous solution

TABLE 1

Time(min)	A1(%)	B1(%)
0	4	96
2	96	4
4	96	4

run time 4.0 min
flow 0.5 mL/min

Method B:

Achiral Reversed-phase-UPLC:

Apparatus: Waters ACQUITY Ultra Performance LC (HPLC™) with TUV Detector and ZQ2000 mass spectrometer

Column: Waters ACQUITY HPLC™ BEH C18, 2.1×100 mm, 1.7 μm

Column temperature: 60° C.

Flow rate: 0.7 mL/min

Solvents:

A1: 10 mM ammonium acetate aqueous solution

B1: Acetonitrile

TABLE 2

Eluting program:

Time(min)	A1(%)	B1(%)
0	95	5
0.1	95	5
1.8	5	95
2.3	95	5

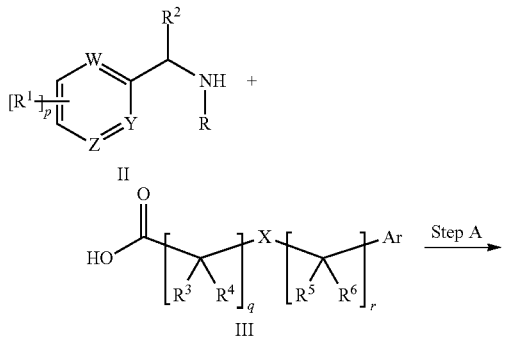
Run time: 3 min

All of the aryl substituted carboxamide derivatives of the formula (I) can be prepared by the procedures described in the general methods presented below or by the specific methods described in the Examples section and the Preparations section, or by routine modifications thereof. The present invention also encompasses any one or more of these processes for preparing the aryl substituted carboxamide derivatives of formula (I), in addition to any novel intermediates used therein.

In the following general methods, Ar, W, X, Y, Z, R^1, R^2, R^3, R^4, R^5, R^6, p, p q and r are as previously defined for aryl substituted carboxamide derivatives of the formula (I) unless otherwise stated.

<Scheme-A>

[Chem. 3]



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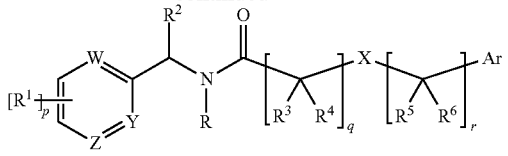


I

In Step A, a compound of formula (I) can be prepared from a compound of formula (III) by amidation with a compound of formula (II) with using a suitable condensation agent such as EDC, preferably under the presence of a base such as a combination of trimethylamine and HOBT, in a suitable solvent such as dichloromethane at a temperature of from 5 to 40° C. for 5-20 hours.

In order to obtain some other compounds of formula (I), the appropriate conversion reaction of the substituents will be used.

For example, alkyl subsituted derivatives can be prepared from a compound of the corresponding halide by coupling reaction with a suitable boronic acid using a suitable catalyst such as tetra kis triphenylphosphine palladium under the presence of a base such as potassium phosphate and a suitable solvent such as dioxane at a temperature of from 5 to 90 ° C. for 12-24 hours; cyclopropane derivatives can be prepared from a compound of the corresponding alphq,beta-unsaturated amide by cyclization reaction with a suitable alkyl diiodide using a suitable reagent such as diethylzinc in a suitable solvent such as dichloromethane at a temperature of from 5 to 90 ° C. for 12-24 hours or by cyclization reaction with a suitable trialkyl sulfoxonium halide such as trimethylsulfoxonium iodide and suitable base such as sodium hydride in a suitable solvent such as DMSO at a temperature of from 5 to 90 ° C. for 1-24 hours; hydroxyl derivatives can be prepared from a compound of the corresponding benzyloxy derivative by hydrogenation with a suitable palladium catalyst such as hydroxyl palladium in a suitable solvent such as ethanol under hydrogen; ether derivatives can be prepared from a compound of the corresponding hydroxyl derivative by alkylation with alkyl alcohol under the presence of a condensation reagent such as di-ter-butyl azodicarboxylate and triphenyl phosphine and base such as N-N-diisopropylethylamine and a suitable solvent such as tetrahydrofuran or with alkyl halide under the presence of a base such as potassium carbonate and a suitable solvent such as dimethylformamide; N-alkylated derivatives can be prepared from a compound of the corresponding NH-amide derivative by alkylation with a suitable alkyl halide using a base such as sodium hydride in a suitable solvent such as dimethylformamide:

All starting materials in the following general syntheses may be commercially available or obtained by conventional methods known to those skilled in the art, otherwise noted in the intermediate synthesis part.

Intermediate Synthesis Part

Amine Intermediate-1

(R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethanamine 2HCl salt

Step-1: 5-(cyclopropylmethoxy)-2-methylpyridine

To a solution of 6-methylpyridin-3-ol (5.0 g, 46 mmol) in DMF (45 mL) were added cesium carbonate (16.5 g, 53 mmol) and (bromomethyl)cyclopropane (7.1 g, 53 mmol) at room temperature. After being stirred at room temperature for 18 hours, the mixture was poured into H_2O, and the aqueous phase was extracted with ethyl acetate (twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (3:1 (v/v)) to give 3.9 g (52% yield) of the title compound as a yellow oil:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (1H, d, J=2.9 Hz), 7.04-7.14 (2H, m), 3.82 (2H, d, J=6.6 Hz), 2.49 (3H, s), 1.21-1.34 (1H, m), 0.67 (2H, q, J=7.3 Hz), 0.37 (2H, q, J=5.9 Hz), LCMS (Method A) m/z: M+1 obs 164.3, tR=2.07 min.

Step-2: (5-(cyclopropylmethoxy)pyridin-2-yl)methanol

To a solution of 5-(cyclopropylmethoxy)-2-methylpyridine (3.9 g, 24 mmol) in dichloromethane (50 mL) was added 3-chlorobenzoperoxoic acid (7.6 g, 32 mmol) at room temperature. After being stirred at room temperature for 1 hour, the mixture was poured into saturated aqueous sodium bicarbonate solution. The organic phase was extracted with dichloromethane (twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in acetic anhydride (50 mL) and the mixture was stirred at 100° C. for 2 hours. Half of the solvent was removed under the reduced pressure. The residue was dissolved into methanol (50 mL). Potassium carbonate (20 g, 143 mmol) was added to the mixture carefully. The mixture was stirred at room temperature for 1 hour. The mixture was poured into H_2O, and the aqueous phase was extracted with ethyl acetate (twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (1:1 (v/v)) to give 4.5 g (quantitative yield) of the title compound as a brown oil:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, d, J=2.9 Hz), 7.21 (1H, dd, J=8.8, 2.9 Hz), 7.17 (1H, d, J=8.8 Hz), 4.70 (2H, s), 3.85 (2H, d, J=7.4 Hz), 1.28 (1H, m), 0.75-0.63 (2H, m), 0.40-0.28 (2H, m), LCMS (Method A) m/z: M+1 obs 180.3, tR=2.09 min.

Step-3: (R,E)-N-((5-(cyclopropylmethoxy)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide

To a solution of (5-(cyclopropylmethoxy)pyridin-2-yl) methanol (4.5 g, 25 mmol) in dichloromethane (50 ml), was added a 15% potassium bromide aqueous solution (20 mL) followed by a saturated bicarbonate solution (20 ml). The biphasic mixture was cooled in an ice bath and TEMPO (200 mg, 1.3 mmol) was added. After stirring for 10 min, 5% sodium hypochlorite (30 ml) was dropwised. The reaction mixture was stirred for 10 min. The solution was poured into a separatory funnel and the organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in dichloromethane (50 mL). Copper(II) sulfate (10.1 g, 63 mmol) followed by (R)-(+)-2-methyl-2-propanesulfinamide (3.1 g, 25 mmol) were added to the mixture respectively and the mixture was stirred for 18 hours at room temperature. The reaction mixture was filtrated off and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (1:1 (v/v)) to give 6.2 g (87% yield) of the title compound as a flaky solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.63 (1H, s), 8.42 (1H, d, J=2.2 Hz), 7.96 (1H, d, J=8.8 Hz), 7.24-7.28 (1H, m), 3.92

(2H, d, J=6.6 Hz), 1.27 (10H, m), 0.67-0.73 (2H, m), 0.39-0.42 (2H, m), LCMS (Method A) m/z: M+1 obs 281.2, tR=2.98 min.

Step-4: (R)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide

A solution of (R,E)-N-((5-(cyclopropylmethoxy)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (6.2 g, 22 mmol) was dissolved into dichloromethane (110 ml). Methyl magnesium bromide (44 ml, 44 mmol, 1.0M in THF) was added to the mixture at −78° C. dropwise. The mixture was stirred for 1 h at −78° C. The mixture was poured into saturated ammonium chloride aqueous solution, and the aqueous phase was extracted with ethyl acetate (twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (1:1 (v/v)) to give 3.2 g (49% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, d, J=2.2 Hz), 7.15-7.23 (2H, m), 4.51-4.57 (2H, m), 3.83 (2H, d, J=6.6 Hz), 1.49 (3H, d, J=6.6 Hz), 1.25 (10H, m), 0.59-0.75 (2H, m) 0.34-0.44 (2H, m), LCMS (Method A) m/z: M+1 obs 297.3, tR=2.81 min.

Step-5: (R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl) ethanamine 2HCl salt

(R)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl) ethyl)-2-methylpropane-2-sulfinamide (3.2 g, 10.9 mmol) was dissolved in 10N HCl/MeOH (50 mL). The mixture was stirred at room temperature for 3 hours. The mixture was concentrated by N_2-flow to give the white precipitate. The solid was collected by filtration and washed with diisopropyl ether to give 3.2 g (49% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.67 (3H, brs), 8.41 (1H, d, J=2.2 Hz), 7.70-7.55 (2H, m), 4.56 (1H, m), 4.01 (2H, d, J=7.3 Hz), 1.57 (3H, d, J=6.6 Hz), 1.33 (1H, m), 0.70-0.60 (2H, m), 0.45-0.35 (2H, m), LCMS (Method A) m/z: M_+1 obs 193.3, tR=1.90 min.

Amine Intermediate-2

(R)-1-(5-(benzyloxy)pyridin-2-yl)ethanamine 2HCl salt

Step-1: (R,E)-N-((5-(benzyloxy)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide

Prepared as in Step 3 of Amine intermediate-1 from (5-(benzyloxy)pyridin-2-yl)methanol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.64 (1H, s), 8.49 (1H, d, J=2.94 Hz), 7.97 (1H, d, J=8.1Hz), 7.31-7.45 (6H, m), 5.19 (2H, s), 1.27 (9H, s), LCMS (Method A) m/z: M+1 obs 317.2, tR=3.15 min.

Step-2: (R)-N-((R)-1-(5-(benzyloxy)pyridin-2-yl) ethyl)-2-methylpropane-2-sulfinamide

Prepared as in Step-4 of Amine intermediate-1 from (R,E)-N-((5-(benzyloxy)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ8.31 (1H, d, J=2.2 Hz), 7.50-7.30 (5H, m), 7.23 (2H, d, J=2.2 Hz), 5.09 (2H, s), 4.57 (2H, m), 1.49 (3H, d, J=6.6 Hz), 1.25 (9H, s), LCMS (Method A) m/z: M+1 obs 333.2, tR=2.97 min.

Step-3: (R)-1-(5-(benzyloxy)pyridin-2-yl)ethanamine 2HCl salt

Prepared as in Step-5 of Amine intermediate-1 from (R)-N-((R)-1-(5-(benzyloxy)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.50 (2H, brs), 8.38 (1H, d, J=2.9 Hz), 7.65-6.25 (7H, m), 6.01 (2H, brs), 5.22 (2H, s), 4.45 (1H, m), 1.46 (3H, d, J=6.6 Hz), LCMS (Method A) m/z: M+1 obs 229.3, tR=2.24 min.

Amine Intermediate-3

(R)-1-(5-(2-fluorobenzyloxy)pyridin-2-yl)ethanamine 2HCl salt

Step-1: 5-(2-fluorobenzyloxy)picolinonitrile

To a mixture of 2-bromo-5-(2-fluorobenzyloxy)pyridine (1.5 g, 5.3 mmol) and zinc cyanide (0.81 g, 6.9 mmol) in DMF (20 mL) was added Tetrakis(triphenylphosphine)palladium (0) (0.61 g, 0.53 mmol) at room temperature. After being stirred at 60° C. for 4 hours, sat. sodium bicarbonate aqueous solution was added to the mixture. The mixture was filtered off through a pad of Celite. The filtrate was extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (2:1 (v/v)) to give 0.69 g (57% yield) of the title compound as a light yellow solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, d, J=2.9 Hz), 7.65 (1H, d, J=8.7 Hz), 7.50-7.28 (3H, m), 7.24-7.05 (2H, m), 5.24 (2H, s), LCMS (Method A) m/z: M+1 obs 229.3, tR=2.94 min.

Step-2: (R,E)-N-((5-(2-fluorobenzyloxy)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide

To a solution of Reactant 5-(2-fluorobenzyloxy)picolinonitrile (690 mg, 3.0 mmol) in dichloromethane (20 mL) was added DIBAL-H (3.7 mL, 3.6 mmol, 0.99 M) at −78° C. After being stirred at −78° C. for 4 hours, methanol (2 mL) was added to the mixture. 1N hydrochloric acid (0.5 mL) was added to the mixture at room temperature. The mixture was stirred at room temperature for 1 hour. Sat. sodium bicarbonate aqueous solution was added to the mixture until the pH was neutrized. The organic layer was extracted with dichloromethane, dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in dichloromethane (20 mL). Copper(II) sulfate (1.2 g, 7.6 mmol) followed by (R)-(+)-2-methyl-2-propanesulfinamide (370 mg, 3.0 mmol) were added to the mixture respectively and the mixture was stirred for overnight at room temperature. The reaction mixture was filtrated off through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (2:1 (v/v)) to give 360 mg (36% yield) of the title compound as a colorless oil:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.64 (1H, s), 8.49 (1H, d, J=2.9 Hz), 7.98 (1H, d, J=8.8 Hz), 7.49 (1H, td, J=7.3, 1.5 Hz), 7.40-7.30 (2H, m), 7.23-7.05 (2H, m), 5.26 (2H, s), 1.27 (9H, s), LCMS (Method A) m/z: M+1 obs 335.3, tR=3.14 min.

Step-3: (R)-N-((R)-1-(5-(2-fluorobenzyloxy)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide

Prepared as in Step-4 of Amine intermediate-1 from (R,E)-N-((5-(2-fluorobenzyloxy)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, d, J=1.4 Hz), 7.48 (1H, t, J=7.3 Hz), 7.40-7.05 (5H, m), 5.16 (2H, s), 4.60-4.50 (2H, m), 1.49 (3H, d, J=5.9 Hz), 1.25 (9H, s), LCMS (Method A) m/z: M+1 obs 351.3, tR=2.97 min.

Step-4: (R)-1-(5-(2-fluorobenzyloxy)pyridin-2-yl) ethanamine 2HCl salt

Prepared as in Step-5 of Amine intermediate-1 from (R)-N-((R)-1-(5-(2-fluorobenzyloxy)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide

^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.97 (2H, brs), 8.40 (1H, m), 7.87 (1H, d, J=8.8 Hz), 7.64 (1H, d, J=8.8 Hz), 7.55-7.35 (2H, m), 7.30-7.08 (2H, m), 5.24 (2H, s), 4.78 (1H, m), 1.76 (3H, d, J=6.6 Hz), LCMS (Method A) m/z: M+1 obs 247.3, tR=2.34 min.

Amine Intermediate-4

(R)-1-(6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine

Step-1: 2,6-dimethyl-3-(2,2,2-trifluoroethoxy)pyridine

Prepared as in Step-1 of Amine intermediate-1 from 2,6-dimethylpyridin-3-ol and 2,2,2-trifluoroethyl trifluoromethanesulfonate.

To a suspension of 2,6-dimethylpyridin-3-ol (5.0 g, 41 mmol) and cesium carbonate (15 g, 47 mmol) in DMF (50 mL) was added 2,2,2-trifluoroethyl trifluoromethane-sulfonate (11 mL, 47 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 hour. After being stirred at room temperature for 18 hours, the mixture was poured into H_2O, and the aqueous phase was extracted with ethyl acetate (twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo to give 8.3 g (quantitative yield) of the title compound as a brown oil:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.01 (1H, d, J=8.0 Hz), 6.95 (1H, d, J=8.0 Hz), 4.33 (2H, q, J=8.0 Hz), 2.48 (6H, s), LCMS (Method A) m/z: M+1 obs 206.2, tR=2.58 min.

Step-2: (6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol

Prepared as in Step-2 of Amine intermediate-1 from 2,6-dimethyl-3-(2,2,2-trifluoroethoxy)pyridine as a minor product.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.12 (1H, d, J=8.0 Hz), 7.08 (1H, d, J=8.0 Hz), 4.68 (2H, s), 4.37 (2H, q, J=8.0 Hz), 2.52 (3H, s), 2.05 (1H, brs) (minor product).

Step-3: (R,E)-2-methyl-N-((6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylene)propane 2-sulfinamide

Prepared as in Step-3 of Amine intermediate-1 from (6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.63 (1H, s), 7.89 (1H, d, J=8.1Hz), 7.16 (1H, d, J=8.1Hz), 4.44 (2H, q, J=8.1Hz), 2.58 (3H, s), 1.27 (9H, s), LCMS (Method A) m/z: M+1 obs 323.2, tR=3.00 min.

Step-4: (R)-2-methyl-N-((R)-1-(6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propane-2-sulfinamide

Prepared as in Step-4 of Amine intermediate-1 from (R,E)-2-methyl-N-((6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylene)propane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (1H, d, J=8.0 Hz), 7.05 (1H, d, J=8.0 Hz), 4.79 (1H, d, J=5.1Hz), 4.55 (1H, m), 4.33 (2H, q, J=8.1Hz), 2.42 (3H, s), 1.48 (3H, d, J=6.6 Hz), 1.25 (9H, s).

Step-5: (R)-1-(6-methyl-5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethanamine 2HCl salt

Prepared as in Step-5 of Amine intermediate-1 from (R)-2-methyl-N-((R)-1-(6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propane-2-sulfinamide. LCMS (Method A) m/z: M+1 obs 235.3, tR=2.24 min.

Amine Intermediate-5

(R)-1-(6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine

Step-1: (6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol

Prepared as in Step-2 of Amine intermediate-1 from 2,6-dimethyl-3-(2,2,2-trifluoroethoxy)pyridine as a major product.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.03-7.09 (2H, m), 4.74 (2H, d, J=4.4 Hz), 4.36 (2H, q, J=8.1Hz), 2.52 (3H, s), 1.64 (1H, brs), LCMS (Method A) m/z: M+1 obs 222.3, tR=2.17 min.

Step-2: (R,E)-2-methyl-N-((6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylene)propane-2-sulfinamide

Prepared as in Step-3 of Amine intermediate-1 from (6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.95 (1H, s), 7.28 (2H, m), 4.44 (2H, m), 2.60 (3H, s), 1.27 (9H, s), LCMS (Method A) m/z: M+1 obs 323.2, tR=2.84 min.

Step-3: (R)-2-methyl-N-((R)-1-(6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propane-2-sulfinamide

Prepared as in Step-4 of Amine intermediate-1 from (R,E)-2-methyl-N-((6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylene)propane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.04 (1H, d, J=8.1Hz), 6.99 (1H, d, J=8.1Hz), 5.21 (1H, d, J=7.3 Hz), 4.86 (1H, m), 4.38 (2H, q, J=8.0 Hz), 2.48 (3H, s), 1.41 (3H, d, J=6.6 Hz), 1.26 (9H, s)

Step-4: (R)-1-(6-methyl-3-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethanamine 2HCl salt

Prepared as in Step-5 of Amine intermediate-1 from (R)-2-methyl-N-((R)-1-(6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$-DMSO-d_6) δ 8.43 (3H, brs), 7.60 (1H, d, J=8.8 Hz), 7.32 (1H, d, J=8.1Hz), 4.91 (2H, q, J=8.8 Hz), 4.54 (1H, m), 2.48 (3H, s), 1.41 (3H, d, J=6.6 Hz).

Amine Intermediate-6

(R)-1-(6-(2-fluorobenzyloxy)pyridin-3-yl)ethanamine

Step-1: (R,E)-N-((6-(2-fluorobenzyloxy)pyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide

To a suspension of sodium hydride (640 mg, 16 mmol, 60%) in DMF (20 mL) was added (2-fluorophenyl)methanol (1.9 g, 15 mmol) at 0° C. After being stirred at room temperature for 30 min, 6-chloronicotinonitrile (2.6 g, 19 mmol) was added to the mixture. The mixture was stirred at room temperature for 14 hours. The mixture was poured into saturated ammonium chloride aqueous solution, and the aqueous phase was extracted with ethyl acetate (twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (19:1 (v/v)) to give the intermediate. The intermediate was dissolved into dichloromethane (30 mL). DIBAL-H (6.3 mL, 6.4 mmol, 0.99 M) was added to the mixture at −78° C. After being stirred at −78° C. for 4 hours, methanol (2 mL) was added to the mixture. 1N hydrochloric acid (0.5 mL) was added to the mixture at room temperature. The mixture was stirred at room temperature for 1 hour. Sat. sodium bicarbonate aqueous solution was added to the mixture until the pH was neutrized. The organic layer was extracted with dichloromethane, dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in dichloromethane (20 mL). Copper(II) sulfate (2.3 g, 14 mmol) followed by (R)-(+)-2-methyl-2-propanesulfinamide (700 mg, 5.8 mmol) were added to the mixture respectively and the mixture was stirred for 18 hours at room temperature. The reaction mixture was filtrated off through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (4:1 (v/v)) to give 155 mg (3% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.55-8.62 (2H, m), 8.14 (1H, dd, J=8.0 Hz), 7.30-7.53 (2H, m), 7.07-7.18 (1H, m), 6.89 (1H, d, J=8.8 Hz), 5.53 (2H, s), 1.26 (9H, s).

Step-2: (R)-N-((R)-1-(6-(2-fluorobenzyloxy)pyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide

Prepared as in Step-4 of Amine intermediate-1 from (R,E)-N-((6-(2-fluorobenzyloxy)pyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, s), 7.51-7.58 (2H, m), 7.29-7.33 (1H, m), 7.06-7.18 (2H, m), 6.80 (1H, d, J=8.0 Hz), 5.44 (2H, s), 4.55-4.59 (2H, m), 1.54 (3H, d, J=6.6 Hz), 1.20 (9H, s).

Step-3: (R)-1-(6-(2-fluorobenzyloxy)pyridin-3-yl) ethanamine 2HCl salt

Prepared as in Step-5 of Amine intermediate-1 from (R)-N-((R)-1-(6-(2-fluorobenzyloxy)pyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$-DMSO-d_6) δ 8.60 (2H, brs), 8.31 (1H, d, J=3.0 Hz), 7.96 (1H, dd, J=2.2 Hz), 7.51-7.61 (1H, m), 7.38-7.45 (1H, m), 7.20-7.27 (2H, m), 6.76 (1H, d, J=8.0 Hz), 6.49 (2H, m), 5.41 (2H, s), 4.40-4.44 (1H, m), 1.53 (3H, d, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 247.3, tR=2.44 min.

Amine Intermediate-7

(R)-1-(5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)ethanamine 2HCl salt

Step-1: 2-methyl-5-((1-methylcyclopropyl)methoxy)pyridine

To a solution of 6-methylpyridin-3-ol (0.5 g, 4.6 mmol) in toluene (6 mL) was added (1-methylcyclopropyl)methanol (0.59 g, 6.9 mmol) and stirred under nitrogen atmosphere. The solution was added cyanomethylenetri-n-butylphosphorane (CMBP, 2.5 ml, 9.53 mmol) and stirred at 100° C. for 3 hours. The reaction mixture was evaporated. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (2:1 (v/v)) to give 820 mg (quantitative yield) of the title compound as a brown oil:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18 (1H, d, J=2.9 Hz), 7.03-7.13 (2H, m), 3.74 (2H, s), 2.48 (3H, s) 1.24 (3H, s), 0.31-0.56 (4H, m), LCMS (Method A) m/z: M+1 obs 178.3, tR=2.54 min.

Step-2: (5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)methanol

Prepared as in Step-2 of Amine intermediate-1 from 2-methyl-5-((1-methylcyclopropyl)methoxy)pyridine.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, d, J=1.4 Hz), 7.16-7.27 (2H, m), 4.70 (2H, s), 3.78 (2H, s), 2.83 (1H, brs), 1.25 (3H, s), 0.45-0.58 (4H, m), LCMS (Method A) m/z: M+1 obs 194.32, tR=2.37 min.

Step-3: (R,E)-2-methyl-N-((5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)methylene)propane-2-sulfinamide

Prepared as in Step-3 of Amine intermediate-1 from (5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)methanol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.64 (1H, s), 8.42 (1H, d, J=2.9 Hz), 7.96 (1H, d, J=8.8 Hz), 7.24 (1H, d, J=2.9 Hz), 3.85 (2H, s), 1.28 (9H, s), 1.24 (3H, s), 0.51-0.59 (4H, m), LCMS (Method A) m/z: M+1 obs 295.3, tR=3.14 min.

Step-4: (R)-2-methyl-N-((R)-1-(5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)ethyl)propane-2-sulfinamide

Prepared as in Step-4 of Amine intermediate-1 from (R,E)-2-methyl-N-((5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)methylene)propane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, d, J=2.2 Hz), 7.13-7.22 (2H, m), 4.52-4.56 (2H, m), 3.75 (2H, s), 1.49 (3H, d, J=6.6 Hz), 1.25 (9H, s), 1.23 (3H, s) 0.44-0.56 (4H, m), LCMS (Method A) m/z: M+1 obs 311.3, tR=2.95 min.

Step-5: (R)-1-(5-((1-methylcyclopropyl)methoxy) pyridin-2-yl)ethanamine 2HCl salt

Prepared as in Step-5 of Amine intermediate-1 from (R)-2-methyl-N-((R)-1-(5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)ethyl)propane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$-DMSO-d_6) δ 8.52 (2H, brs), 8.34 (1H, s), 7.52 (2H, s), 5.80 (2H, brs), 4.48 (1H, m), 3.88

(2H, s), 1.49 (3H, d, J=6.6 Hz), 1.19 (3H, s), 0.41-0.56 (4H, m), LCMS (Method A) m/z: M+1 obs 207.3, tR=2.07 min.

Amine Intermediate-8

3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinolin-8-amine

Step-1: 3-(2,2,2-trifluoroethoxy)quinoline

Prepared as in Step-1 of Amine intermediate-4 from quinolin-3-ol.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.77 (1H, d, J=2.9 Hz), 8.08 (1H, d, J=8.0 Hz), 7.75 (1H, d, J=8.1Hz), 7.67-7.50 (2H, m), 7.45 (1H, d, J=2.9 Hz), 4.50 (2H, q, J=8.0 Hz), LCMS (Method A) m/z: M+1 obs 228.3, tR=2.90 min.

Step-2: 3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinoline

A mixture of 3-(2,2,2-trifluoroethoxy)quinoline (1.13 g, 5.0 mmol) and platinum (IV) oxide (50 mg) in TFA (8 mL) was stirred at room temperature for 12 hours under hydrogen atmosphere (1 atm). Then the mixture was filtered off through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10:1-7:1) to give 495 mg (43% yield) of the title compound as a colorless oil:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.12 (1H, d, J=2.9 Hz), 6.96 (1H, d, J=2.9 Hz), 4.36 (2H, q, J=8.1Hz), 2.87 (2H, t, J=6.6 Hz), 2.77 (2H, t, J=6.6 Hz), 1.93-1.75 (4H, m), LCMS (Method A) m/z: M+1 obs 232.3, tR=2.84 min.

Step-3: 3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinoline 1-oxide

A mixture of 3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinoline (495 mg, 2.1 mmol) and 3-chloroperbenzoic acid (ca 75%, 739 mg, 3.2 mmol) in dichloromethane (10 mL) was stirred at room temperature for 1.5 hour. Then, the mixture was poured into saturated sodium bicarbonate aqueous solution (50 mL), and the aqueous phase was extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated in vacuo to give 740 mg of the crude title compound. This was used for the next step without further purification:

LCMS (Method A) m/z: M+1 obs 248.3, tR=2.52 min.

Step-4: 3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinolin-8-ol

A mixture of 3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinoline 1-oxide (530 mg, 2.1 mmol) and acetic anhydride (3 mL) was stirred at 100° C. for 2 hours. After cooling to room temperature, acetic anhydride was removed in vacuo. To the residue, methanol (5 mL) and potassium carbonate (1.77 g, 13 mmol) were added, and the mixture was stirred at room temperature for 20 hours. Then, methanol was evaporated in vacuo. To the residue was added ethyl acetate, and the mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (1:1-1:2) to give 193 mg (36% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.17 (1H, d, J=2.9 Hz), 7.00 (1H, d, J=2.9 Hz), 4.69 (1H, brt, J=5.9 Hz), 4.38 (2H, q, J=8.1Hz), 3.64 (1H, s), 2.85-2.75 (2H, m), 2.31-2.20 (1H, m), 2.05-1.94 (1H, m), 1.88-1.75 (2H, m), LCMS (Method A) m/z: M+1 obs 248.2, tR=2.52 min.

Step-5: 3-(2,2,2-trifluoroethoxy)-6,7-dihydroquinolin-8(5H)-one

A mixture of 3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinolin-8-ol (193 mg, 0.78 mmol) and manganese (IV) oxide (543 mg, 6.3 mmol) in dichloromethane (10 mL) was stirred at room temperature for 3 hours. Then, the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residual solid was washed with diethyl ether to give 155 mg (81% yield) of the title compound as a pale yellow solid:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.44 (1H, d, J=2.9 Hz), 7.11 (1H, d, J=2.9 Hz), 4.48 (2H, q, J=8.1Hz), 3.03 (2H, t, J=5.9 Hz), 2.79 (2H, t, J=5.9 Hz), 2.20 (2H, quintet, J=5.9 Hz), LCMS (Method A) m/z: M+1 obs 246.3, tR=2.48 min.

Step-6: 3-(2,2,2-trifluoroethoxy)-6,7-dihydroquinolin-8(5H)-one oxime

A mixture of 3-(2,2,2-trifluoroethoxy)-6,7-dihydroquinolin-8(5H)-one (155 mg, 0.63 mmol), hydroxylamine hydrochloride (88 mg, 1.3 mmol), and sodium acetate (104 mg, 1.3 mmol) in ethanol-water (3:1, 4 mL) was refluxed with stirring for 2 hours. After cooling to room temperature, the mixture was poured into water, and the aqueous layer was extracted with dichloromethane (twice). The combined organic layers were dried over Magnesium sulfate and concentrated in vacuo to give 167 mg of the crude title compound as a brown solid. This was used for the next step without purification:

^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.25 (1H, d, J=2.9 Hz), 7.37 (1H, d, J=2.9 Hz), 4.88 (2H, q, J=8.8 Hz), 2.79-2.68 (2H, m), 1.95-1.75 (4H, m) (a signal due to OH was not observed), LCMS (Method A) m/z: M+1 obs 261.3, tR=2.62 min.

Step-7: 3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinolin-8-amine

A mixture of 3-(2,2,2-trifluoroethoxy)-6,7-dihydroquinolin-8(5H)-one oxime (167 mg) and 10% palladium on carbon (100 mg) in methanol (7 mL) was stirred at room temperature for 24 h under hydrogen atmosphere (4 atm). Then, the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on NH-gel eluting with hexane/ethyl acetate (1:1-0:1) to give 68 mg (43% yield) of the title compound as a pale brown oil:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.18 (1H, s), 7.96 (1H, s), 4.37 (2H, q, J=8.1Hz), 4.03-3.95 (1H, m), 2.90-2.68 (2H, m), 2.24-2.13 (1H, m), 2.03-1.90 (1H, m), 1.85-1.66 (2H, m) (a signals due to NH2 were not observed), LCMS (Method A) m/z: M+1 obs 247.3, tR=2.14 min.

Amine Intermediate-9

(R)-1-(3-fluoro-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine 2HCl salt

Step-1:
3-fluoro-5-(2,2,2-trifluoroethoxy)picolinonitrile

60% sodium hydride (0.219 g, 5.71 mmol) was added to a solution of 2,2,2-trifluoroethanol (0.257 ml, 3.57 mmol) in N,N,N',N',N",N"-hexamethylphosphoric triamide (6 ml) at 0 oC and stirred for 1 hour. Then 3,5-difluoropicolinonitrile

(1.0 g, 7.1 mmol) in N,N,N',N',N",N"-hexamethylphosphoric triamide (4 mL) was added to the reaction mixture and stirred at room temperature for 20 hours. Then 2,2,2-trifluoroethanol (0.257 ml, 3.57 mmol) and 60% sodium hydride (0.22 g, 5.7 mmol) were added to the reaction mixture and stirred at room temperature for 3 hours. After reaction, the mixture was poured into water, and the aqueous phase was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (6:1-4:1) to give 398 mg (25% yield) of the title compound as a oily solution:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, d, J=2.6 Hz), 7.15 (1H, dd, J=9.5, 2.6 Hz), 4.50 (2H, q, J=7.7 Hz).

Step-2: (R,E)-N-((3-fluoro-5-(2,2,2-trifluoroethoxy) pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide

Prepared as in Step-2 of Amine intermediate-3 from 3-fluoro-5-(2,2,2-trifluoroethoxy)picolinonitrile.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.83 (1H, s) 8.39 (1H, d, J=2.2 Hz), 7.11 (1H, dd, J=2.2 Hz), 4.89 (2H, q, J=7.4 Hz), 1.30 (9H, s), LCMS (Method A) m/z: M+1 obs 327.2, tR=2.94 min.

Step-3: (R)-N-((R)-1-(3-fluoro-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide

Prepared as in Step-4 of Amine intermediate-1 from (R,E)-N-((3-fluoro-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, s), 7.02 (1H, dd, J=1.5, 2.2 Hz), 4.70-4.88 (2H, m), 4.38 (2H, q, J=6.6 Hz), 1.45 (3H, d, J=6.6 Hz), 1.25 (9H, s), LCMS (Method A) m/z: M+1 obs 343.2, tR=2.92 min.

Step-4: (R)-1-(3-fluoro-5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethanamine 2HCl salt

Prepared as in Step-5 of Amine intermediate-1 from (R)-N-((R)-1-(3-fluoro-5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)-2-methylpropane-2-sulfinamide.

LCMS (Method A) m/z: M+1 obs 222.3, tR=2.00 min.

Amine Intermediate-10

(R)-1-(3-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine dihydrochloride

Step-1: 3-methyl-5-(2,2,2-trifluoroethoxy)picolinonitrile

Prepared as in Step-1 of Amine intermediate-4 from commercially available 5-hydroxy-3-methylpicolinonitrile:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, d, J=2.9 Hz), 7.18 (1H, d, J=2.9 Hz), 4.46 (2H, q, J=7.4 Hz), 2.58 (3H, s), LCMS (Method A) m/z: M+1 obs 217.3, tR=2.79 min.

Step-2: (R,E)-2-methyl-N-((3-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylene)propane-2-sulfinamide

Prepared as in Step-2 of Amine intermediate-3 from 3-methyl-5-(2,2,2-trifluoroethoxy)picolinonitrile.

LCMS (Method A) m/z: M+1 obs 323.3, tR=3.02 min.

Step-3: (R)-2-methyl-N-((R)-1-(3-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propane-2-sulfinamide

Prepared as in Step-4 of Amine intermediate-1 from (R,E)-2-methyl-N-((3-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methylene)propane-2-sulfinamide:

^{1}H-NMR (270 MHz, $CDCl_3$): δ 8.13 (1H, d, J==3.3 Hz), 7.05 (1H, d, J=3.3 Hz), 4.88 (1H, d, J=7.2 Hz), 4.69 (1H, quintet, J=6.5 Hz), 4.38 (2H, q, J=7.9 Hz), 2.38 (3H, s), 1.39 (3H, d, J=6.6 Hz), 1.25 (9H, s), LCMS (Method A) m/z: M+1 obs 339.3, tR=2.95 min.

Step-4: (R)-1-(3-methyl-5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethanamine dihydrochloride

Prepared as in Step-5 of Amine intermediate-1 from (R)-2-methyl-N-((R)-1-(3-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propane-2-sulfinamide:

LCMS (Method A) m/z: M+1 obs 235.3, tR=2.20 min.

Amine Intermediate-11

(S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine dihydrochloride

The title compound was prepared according to the silimar procedure for (R)-isomer using (S)-(−)-2-methyl-2-propanesulfinamide:

$[\alpha]D^{22}$ −16.7°(c=1.61, MeOH).

Carboxylic Acid Intermediate-1

1-methyl-6-(trifluoromethyl)-1H-indazole-3-carboxylic acid

Step-1: methyl 1-methyl-6-(trifluoromethyl)-1H-indazole-3-carboxylate

To an acetonitrile (5 ml) solution of methyl 6-(trifluoromethyl)-1H-indazole-3-carboxylate (300 mg, 1.2 mmol) were added potassium carbonate (1.0 g, 7.4 mmol) and iodomethane (350 mg, 2.5 mmol) at room temperature respectively. The mixture was stirred at room temperature for 4 hours. The solid was removed by filtration and washed with acetonitrile. The filtrate was concentrated in vacuo. After being filtered off, the filtrate was concentrated under reduced pressure, the residue was applied to a silica gel chromatography column and eluted with a hexane/ethyl acetate=4/1 to furnish 239 mg (75% yield, major product) of the title as a white solid;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.36 (1H, d, J=8.0 Hz), 7.79 (1H, s), 7.55 (1H, d, J=8.0 Hz), 4.24 (3H, s), 4.06 (3H, s), LCMS (Method A) m/z: M+1 obs 259.1; tR=3.15 min.

Step-2: 1-methyl-6-(trifluoromethyl)-1H-indazole-3-carboxylic acid

To a tetrahydrofuran (2 mL) of methyl 1-methyl-6-(trifluoromethyl)-1H-indazole-3-carboxylate (50 mg, 0.19 mmol) was added 2N sodium hydroxide (0.2 ml, 4.0 mmol) at room temperature. The mixture was refluxed at 90° C. with stirring for 3 hours. After being cooled to room temperature, 2N hydrochloric acid was added to the mixture until pH became 4.0. The organic layer was extracted with ethyl acetate,

washed with brine, and dried over magnesium sulfate. After the filtration to separate solvent and magnesium sulfate, the solvent was removed under reduced pressure to give 47 mg (quantitative yield) of the title as a white solid that was used in the next step without further purification;

LCMS (Method A) m/z: M+1 obs 245.0; tR=2.57 min.

Carboxylic Acid Intermediate-2

2-methyl-6-(trifluoromethyl)-2H-indazole-3-carboxylic acid

Step-1: methyl 2-methyl-6-(trifluoromethyl)-2H-indazole-3-carboxylate

Prepared as in Step 1 of Carboxylic acid intermediate-1 as a minor product.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13 (1H, d, J=8.8 Hz), 8.10 (1H, s), 7.45 (1H, d, J=8.8 Hz), 4.56 (3H, s), 4.06 (3H, s), LCMS (Method A) m/z: M+1 obs 259.1, tR=2.99 min.

Step-2: 2-methyl-6-(trifluoromethyl)-2H-indazole-3-carboxylic acid

Prepared as in Step 2 of Carboxylic acid intermediate-1 from methyl 2-methyl-6-(trifluoromethyl)-2H-indazole-3-carboxylate.

LCMS (Method A) m/z: M+1 obs 245.0, tR=2.52 min.

Carboxylic Acid Intermediate-3

1-methyl-6-(trifluoromethyl)-1H-indole-2-carboxylic acid

Step-1: ethyl 1-methyl-6-(trifluoromethyl)-1H-indole-2-carboxylate

A mixture of ethyl 6-(trifluoromethyl)-1H-indole-2-carboxylate (100 mg, 0.39 mmol), iodomethane (36 microL, 0.58 mmol), and potassium carbonate (134 mg, 0.97 mmol) in DMF was stirred at room temperature for 7 hours. Then, the mixture was poured into water, and the aqueous layer was extracted with dichloromethane (three times). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (20:1-10:1) to give 95.3 mg (90% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.98 (1H, s), 7.56 (1H, d, J=8.8 Hz), 7.47 (1H, d, J=8.8 Hz), 7.37 (1H, s), 4.40 (2H, q, J=7.4 Hz), 4.11 (3H, s), 1.43 (3H, t, J=7.4 Hz), LCMS (Method A) m/z: M+1 obs 272.1, tR=3.45 min.

Step-2: 1-methyl-6-(trifluoromethyl)-1H-indole-2-carboxylic acid

A mixture of ethyl 1-methyl-6-(trifluoromethyl)-1H-indole-2-carboxylate (90 mg, 0.33 mmol) and 2 mol/L aqueous sodium hydroxide solution (0.42 mL, 0.83 mmol) in methanol (2 mL) was stirred at room temperature for 2 hours. Then, 2 mol/L hydrochloric acid was added, and the formed precipitate was collected by filtration to give 75.6 mg (94% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.23 (1H, br), 8.12 (1H, s), 7.80 (1H, d, J=8.8 Hz), 7.60 (1H, d, J=8.8 Hz), 7.39 (1H, s), 4.08 (3H, s), LCMS (Method A) m/z: M−1 obs 242.1, tR=2.88 min.

Carboxylic Acid Intermediate-4

1-methyl-6-(trifluoromethyl)-1H-indole-3-carboxylic acid

Step-1: 2,2,2-trifluoro-1-[6-(trifluoromethyl)-1H-indol-3-yl]ethanone

To a solution of 6-(trifluoromethyl)-1H-indole (460 mg, 2.5 mmol) in tetrahydrofuran (5 mL) was added trifluoroacetic anhydride (0.52 mL, 3.7 mmol) at 0° C., and the resulting mixture was stirred at the same temperature for 1 hour and at room temperature for 1 hour. Then, the mixture was poured into water, and the formed precipitate was collected by filtration to give 583 mg (83% yield) of the title compound as a pale brown solid:

^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.04 (1H, br), 8.72 (1H, s), 8.37 (1H, d, J=8.8 Hz), 7.93 (1H, s), 7.66 (1H, d, J=8.1Hz), LCMS (Method A) m/z: M−1 obs 280.0, tR=3.20 min.

Step-2: 2,2,2-trifluoro-1-(1-methyl-6-(trifluoromethyl)-1H-indol-3-yl)ethanone

To a mixture of 2,2,2-trifluoro-1-[6-(trifluoromethyl)-1H-indol-3-yl]ethanone (200 mg, 0.71 mmol) and potassium carbonate (246 mg, 1.8 mmol) in DMF (2 mL) was added iodomethane (0.067 mL, 1.1 mmol) at room temperature. After stirring at the same temperature for 2 hours, the mixture was poured into water, and the aqueous phase was extracted with EtOAc (ethyl acetate)-hexane (2:1, twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (4:1 (v/v)) to give 195 mg (93% yield) of the title compound as a pale brown solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (1H, d, J=8.0 Hz), 8.04 (1H, s), 7.70 (1H, s), 7.64 (1H, d, J=8.1Hz), 3.99 (3H, s), LCMS (Method A) m/z: M+1 obs 296.0, tR=3.32 min.

Step-3: 1-methyl-6-(trifluoromethyl)-1H-indole-3-carboxylic acid

A mixture of 2,2,2-trifluoro-1-(1-methyl-6-(trifluoromethyl)-1H-indol-3-yl)ethanone (195 mg, 0.66 mmol) and 20% aqueous sodium hydroxide solution (5 mL) was refluxed with stirring for 10 hours. After cooling to room temperature, the mixture was poured into 1 M hydrochloric acid, and the aqueous phase was extracted with ethyl acetate (twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residual solid was washed with 2-propanol to give 107 mg (67% yield) of the title compound as a pale orange solid:

^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.25 (1H, s), 8.26 (1H, s), 8.18 (1H, d, J=8.8 Hz), 7.98 (1H, s), 7.50 (1H, d, J=8.6 Hz), 3.94 (3H, s), LCMS (Method A) m/z: M−1 obs 242.1, tR=2.84 min.

Carboxylic Acid Intermediate-5

5-(2,2,2-trifluoroethoxy)picolinic acid

Step-1: ethyl 5-(2,2,2-trifluoroethoxy)picolinate

Prepared as in Step-1 of Amine intermediate-4 from ethyl 5-hydroxypicolinate (EP1748048):

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.47 (1H, d, J=2.9 Hz), 8.15 (1H, d, J=8.8 Hz), 7.32 (1H, dd, J=2.9 & 8.8 Hz), 4.52-5.52 (4H, m), 1.44 (3H, t, J=7.2 Hz), LCMS (Method A) m/z: M+1 obs 250.3, tR=2.72 min.

Step-2: 5-(2,2,2-trifluoroethoxy)picolinic acid

A mixture of ethyl 5-(2,2,2-trifluoroethoxy)picolinate (253 mg, 1.0 mmol) and 2 mol/L aqueous sodium hydroxide solution (1.0 mL, 2.0 mmol) in methanol (5 mL) was stirred at room temperature for 4 h. Then, methanol was removed in vacuo. To the residue were added water (2 mL) and 2 mol/L hydrochloric acid (pH~4). The formed precipitate was collected by filtration to give 118 mg (52% yield) of the title compound as a gray solid:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.49 (1H, d, J=2.9 Hz), 8.06 (1H, d, J=8.8 Hz), 7.66 (1H, dd, J=2.9 & 8.8 Hz), 4.99 (2H, q, J=8.8 Hz) (a signal due to COOH was not observed), LCMS (Method A) m/z: M+1 obs 222.3, tR=1.59 min.

Carboxylic Acid Intermediate-6 trans-2-(1-methyl-1H-indol-3-yl)cyclopropanecarboxylic acid

Step-1: ethyl trans-2-(1-methyl-1H-indol-3-yl)cyclopropanecarboxylate

To a suspension of sodium hydride (ca 60%, 21 mg, 0.52 mmol) in DMSO (1 mL) was added trimethylsulfoxonium iodide (115 mg, 0.52 mmol), and the mixture was stirred at room temperature for 20 minutes. Then, ethyl (E)-3-(1-methyl-1H-indol-3-yl)acrylate (Synlett, (9), 1319-1322 (2006)) (100 mg, 0.44 mmol) was added to the mixture, and the mixture was stirred at room temperature for 1 hour and at 60° C. for 20 hours. After cooling to room temperature, the mixture was poured into water (30 mL), and the aqueous phase was extracted with ethyl acetate (twice). The combined organic layers were dried over Magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (7:1) to give 23 mg (21% yield) of the title compound as a pale yellow oil:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.65 (1H, d, J=8.0 Hz), 7.30-7,19 (2H, m), 7.16-7.07 (1H, m), 6.79 (1H, s), 4.20 (2H, q, J=8.0 Hz), 3.71 (3H, s), 2.65-2.55 (1H, m), 1.91-1.82 (1H, m), 1.61-1.51 (1H, m), 1.30 (3H, t, J=8.0 Hz), 1.35-1.25 (1H, m), LCMS (Method A) m/z: M+1 obs 244.4, tR=3.22 min.

Step-2: trans-2-(1-methyl-1H-indol-3-yl)cyclopropanecarboxylic acid

A mixture of ethyl trans-2-(1-methyl-1H-indol-3-yl)cyclopropanecarboxylate (20 mg, 0.082 mmol) and 2 mol/L aqueous sodium hydroxide solution (0.20 mL, 0.40 mmol) in methanol (3 mL) was stirred at 60° C. for 3 hours. After cooling to room temperature, 2 mol/L hydrochloric acid (0.20 mL, 0.40 mmol) was added, and the solvent was removed in vacuo. To the residue was added THF (2 mL) and filtered off. The filtrate was concentrated in vacuo to give 25 mg of the title compound as a pale yellow oil. This was used for the next step without purification:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.68 (1H, d, J=8.8 Hz), 7.31-7.20 (2H, m), 7.18-7.09 (1H, m), 6.82 (1H, s), 3.73 (3H, s), 2.75-2.64 (1H, m), 1.90-1.80 (1H, m), 1.69-1.60 (1H, m), 1.45-1.35 (1H, m), LCMS (Method A) m/z: M+1 obs 216.4, tR=2.72 min.

Carboxylic Acid Intermediate-7

trans-2-(7-fluoro-1H-indol-3-yl)cyclopropanecarboxylic acid

Step-1: ethyl (E)-3-(7-fluoro-1-tosyl-1H-indol-3-yl) acrylate

To a suspension of sodium hydride (ca 60%, 240 mg, 6.3 mmol) in THF (10 mL) was added dropwise a solution of triethyl phosphonoacetate (1.33 g, 5.9 mmol) in THF (5 mL) at 0° C. After stirring at room temperature for 0.5 hour, a solution of 7-fluoro-1-tos yl-1H-indole-3-carbaldehyde (J. Med. Chem., 48 (19), 6023-6034 (2005)) (1.10 g, 3.48 mmol) in THF (5 mL) was added to the mixture at 0° C. The resulting mixture was stirred at 0° C. for 0.5 hour and at room temperature for 19 hours. The mixture was poured into water, extracted with dichloromethane, dried over sodium sulfate, filtered and concentrated in vacuo. The residual solid was washed with ethyl acetate to give 864 mg (65% yield) of the title compound as a white solid:

^{1}H-NMR (270 MHz, $CDCl_3$): δ 8.03 (1H, s), 7.85-7.75 (3H, m), 7.57 (1H, d, J=7.6 Hz), 7.31-7.15 (3H, m), 6.99 (1H, dd, J=8.2 & 12.2 Hz), 6.50 (1H, d, J=16.1Hz), 4.27 (2H, q, J=7.2 Hz), 2.37 (3H, s), 1.33 (3H, t, J=7.2 Hz).

Step-2: ethyl trans-2-(7-fluoro-1-tos yl-1H-indol-3-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(7-fluoro-1-tosyl-1H-indol-3-yl)acrylate:

^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.78 (2H, d, J=7.6 Hz), 7.45 (1H, s), 7.34 (1H, d, J=6.9 Hz), 7.28-7.22 (2H, m), 7.13 (1H, dt, J=4.3 & 7.9 Hz), 6.94 (1H, dd, J=7.9 & 12.2 Hz), 4.19 (2H, q, J=7.3 Hz), 2.51-2.42 (1H, m), 2.36 (3H, s), 1.92-1.84 (1H, m), 1.61-1.52 (1H, m), 1.30 (3H, t, J=7.3 Hz), 1.33-1.20 (1H, m).

Step-3: trans-2-(7-fluoro-1H-indol-3-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(7-fluoro-1-tos yl-1H-indol-3-yl)cyclopropanecarboxylate:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.16 (1H, brs), 7.44 (1H, d, J=8.0 Hz), 7.1-6.8 (3H, m), 2.71-2.59 (1H, m), 1.95-1.85 (1H, m), 1.70-1.60 (1H, m), 1.48-1.35 (1H, m) (a signal due to COOH was not observed), LCMS (Method A) m/z: M+1 obs 220.3, tR=2.57 min.

Carboxylic Acid Intermediate-8

trans-2-(5-fluoro-1H-indol-3-yl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(5-fluoro-1-tosyl-1H-indol-3-yl) acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 5-fluoro-1-tosyl-1H-indole-3-carbaldehyde (J. Med. Chem., 41 (25), 4995-5001 (1998)):

^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.95 (1H, dd, J=4.6 & 9.2 Hz), 7.86 (1H, s), 7.79-7.68 (3H, m), 7.44 (1H, dd, J=2.6 & 8.6 Hz), 7.29-7.24 (2H, m), 7.11 (1H, dt, J=2.6 & 8.6 Hz), 6.43 (1H, d, J=16.5 Hz), 4.27 (2H, q, J=7.2 Hz), 2.37 (3H, s), 1.35 (3H, t, J=7.2 Hz), LCMS (Method A) m/z: M+1 obs 388.2, tR=3.52 min.

Step-2: ethyl trans-2-(5-fluoro-1-tosyl-1H-indol-3-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(5-fluoro-1-tosyl-1H-indol-3-yl)acrylate:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.93-7.86 (1H, m), 7.71 (2H, d, J=9.5 Hz), 7.30-7.17 (4H, m), 7.09-7.00 (1H, m), 4.20 (2H, q, J=7.3 Hz), 2.46-2.35 (1H, m), 2.35 (3H, s), 1.88-1.80 (1H, m), 1.63-1.55 (1H, m), 1.31 (3H, t, J=7.3 Hz), 1.30-1.20 (1H, m)., LCMS (Method A) m/z: M+1 obs 402.3, tR=3.54 min.

Step-3: trans-2-(5-fluoro-1H-indol-3-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(5-fluoro-1-tosyl-1H-indol-3-yl)cyclopropanecarboxylate:

^{1}H-NMR (300 MHz, DMSO-d_6): δ 11.00 (1H, brs), 7.36-7.22 (3H, m), 6.98-6.88 (1H, m), 2.43-2.33 (1H, m), 1.75-1.67 (1H, m), 1.42-1.28 (2H, m) (a signal due to COON was not observed), LCMS (Method A) m/z: M+1 obs 220.3, tR=2.59 min.

Carboxylic Acid Intermediate-9

trans-2-(1H-indol-6-yl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(1-tosyl-1H-indol-6-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate 7 from 1-tosyl-1H-indole-6-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13 (1H, s), 7.90-7.75 (3H, m), 7.62 (1H, d, J=3.7 Hz), 7.52 (1H, d, J=8.8 Hz), 7.43 (1H, d, J=8.8 Hz), 7.24 (2H, d, J=8.1Hz), 6.66 (1H, d, J=3.7 Hz), 6.49 (1H, d, J=16.1Hz), 4.29 (2H, q, J=7.3 Hz), 2.35 (3H, s), 1.37 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 370.2, tR=3.44 min.

Step-2: ethyl trans-2-(1-tosyl-1H-indol-6-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl(E)-3-(1-tosyl-1H-indol-6-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, J=8.1Hz), 7.76 (1H, s), 7.53 (1H, d, J=3.7 Hz), 7.43 (1H, d, J=8.1Hz), 7.25 (2H, d, J=8.1Hz), 6.97 (1H, dd, J=8.1, 1.5 Hz), 6.62 (1H, d, J=3.7 Hz), 4.21 (2H, q, J=7.3 Hz), 2.67 (1H, m), 2.37 (3H, s), 1.95 (1H, m), 1.67 (1H, m), 1.39 (1H, m), 1.32 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 384., tR=3.44 min.

Step-3: trans-2-(1H-indol-6-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(1-tosyl-1H-indol-6-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.00 (1H, s), 7.44 (1H, d, J=8.0 Hz), 7.29 (1H, t, J=2.2 Hz), 7.18 (1H, s), 6.79 (1H, d, J=8.1Hz), 6.37 (1H, m), 2.50 (1H, m), 1.78 (1H, m), 1.48-1.30 (2H, m), LCMS (Method A) m/z: M−1 obs 200.3, tR=2.52 min.

Carboxylic Acid Intermediate-10

trans-2-(5-cyano-1H-indol-3-yl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(5-cyano-1-tosyl-1H-indol-3-yl) acrylate

Prepared as in Step-1 of Carboxylic acid intermediate 7 from 3-formyl-1-tosyl-1H-indole-5-carbonitrile.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, s), 8.11 (1H, d, J=8.8 Hz), 7.94 (1H, s), 7.81 (2H, d, J=8.1Hz), 7.74 (1H, d, J=16.1Hz), 7.63 (1H, dd, J=8.8, 1.5 Hz), 7.30 (2H, d, J=8.0 Hz), 6.49 (1H, d, J=16.1Hz), 4.29 (2H, q, J=6.6 Hz), 2.39 (3H, s), 1.36 (3H, t, J=6.6 Hz), LCMS (Method A) m/z: M+1 obs 395.2, tR=3.40 min.

Step-2: trans-2-(5-cyano-1H-indol-3-yl)cyclopropanecarboxylic acid

Prepared as in Step-1 of Carboxylic acid intermediate 6 and in Step-2 of Carboxylic acid intermediate 6 from ethyl (E)-3-(5-cyano-1-tosyl-1H-indol-3-yl)acrylate. LCMS (Method A) m/z: M+1 obs 227.3, tR=2.39 min.

Carboxylic Acid Intermediate-11

trans-2-(1H-indol-7-yl)cyclopropanecarboxylic acid

Step-1:1-tosyl-1H-indole-7-carbaldehyde

To a suspension of sodium hydride (240 mg, 5.9 mmol) in THF (10 mL) was added 1H-indole-7-carbaldehyde (570 mg, 3.9 mmol) at room temperature. After being stirred at room temperature for 20 min, 4-methylbenzene-1-sulfonyl chloride (1.1 g, 5.9 mmol) was added to the mixture. The mixture was stirred at room temperature for 1 hour. The mixture was poured into saturated ammonium chloride aqueous solution, and the aqueous phase was extracted with ethyl acetate (twice). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (4:1 (v/v)) to give 1.0 g (89% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.73 (1H, s), 7.82 (1H, d, J=8.8 Hz), 7.75-7.65 (2H, m), 7.47 (2H, d, J=8.8 Hz), 7.38 (1H, t, J=8.3 Hz), 7.17 (2H, d, J=8.8 Hz), 6.79 (1H, d, J=3.7 Hz), 2.34 (3H, s), LCMS (Method A) m/z: M+1 obs 300.2, tR=3.15 min.

Step-2: ethyl(E)-3-(1-tosyl-1H-indol-7-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate 7 from 1-tosyl-1H-indole-7-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.64 (1H, d, J=15.4 Hz), 7.84 (1H, d, J=3.7 Hz), 7.65-7.55 (3H, m), 7.34 (1H, d, J=7.3 Hz), 7.26-7.10 (3H, m), 6.72 (1H, d, J=4.4 Hz), 6.10 (1H, d, J=15.4 Hz), 4.32 (2H, q, J=7.3 Hz), 2.34 (3H, s), 1.41 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 370.3, tR=3.40 min.

Step-3: ethyl trans-2-(1-tosyl-1H-indol-7-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(1-tosyl-1H-indol-7-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (1H, d, J=3.7 Hz), 7.54 (2H, d, J=8.1Hz), 7.38 (1H, d, J=8.9 Hz), 7.21-7.10 (3H, m), 6.91 (1H, d, J=8.0 Hz), 6.67 (1H, d, J=3.7 Hz), 4.29-4.19 (2H, m), 3.17 (1H, m), 2.34 (3H, s), 1.92 (1H, m), 1.48 (1H, m), 1.33 (3H, t, J=6.6 Hz), 1.24 (1H, m), LCMS (Method A) m/z: M+1 obs 384.2, tR=3.42 min.

Step-4:
trans-2-(1H-indol-7-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate 6 from ethyl trans-2-(1-tosyl-1H-indol-7-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.31 (1H, s), 7.39 (1H, d, J=8.1Hz), 7.33 (1H, t, J=1.5 Hz), 6.91 (1H, t, J=7.3 Hz), 6.68 (1H, d, J=7.3 Hz), 6.44 (1H, t, J=1.5 Hz), 2.79 (1H, m), 1.88 (1H, m), 1.51 (1H, m), 1.34 (1H, m), LCMS (Method A) m/z: M−1 obs 200.3, tR=2.62 min.

Carboxylic Acid Intermediate-12

trans-2-(1H-indol-2-yl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(1-tosyl-1H-indol-2-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 1-tosyl-1H-indole-2-carbaldehyde (Heterocycles, 76(2), 1155-1170; 2008).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, d, J=16.1Hz), 8.22 (1H, d, J=8.4 Hz), 7.62 (2H, d, J=8.4 Hz), 7.48 (1H, d, J=8.1Hz), 7.36 (1H, dt, J=7.3, 1.1Hz), 7.26 (1H, m), 7.16 (2H, d, J=8.1Hz), 6.96 (1H, s), 6.36 (1H, d, J=16.1Hz), 4.30 (2H, q, J=7.3 Hz), 2.32 (3H, s), 1.37 (3H, t, J=7.3 Hz).

Step-2: ethyl trans-2-(1-tosyl-1H-indol-2-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl(E)-3-(1-tosyl-1H-indol-2-yl)acrylate:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (1H, d, J=8.1Hz), 7.73 (2H, d, J=8.1Hz), 7.42-7.19 (5H, m), 6.28 (1H, s), 4.28-4.11 (2H, m), 2.93 (1H, m), 2.34 (3H, s), 1.82 (1H, m), 1.62 (1H, m), 1.35-1.22 (4H, m).

Step-3:
trans-2-(1H-indol-2-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(1-tosyl-1H-indol-2-yl)cyclopropanecarboxylate:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, s), 7.49 (1H, d, J=7.3 Hz), 7.23 (1H, d, J=8.8 Hz), 7.10 (2H, m), 6.14 (1H, s), 2.60 (1H, m), 1.92 (1H, m), 1.62 (1H, m), 1.41 (1H, m), LCMS (Method A) m/z: M+1 obs 202.3, tR=2.59 min.

Carboxylic Acid Intermediate-13

trans-2-(5-fluoro-1H-indol-2-yl)cyclopropanecarboxylic acid

Step-1: 5-fluoro-N-methoxy-N-methyl-1H-indole-2-carboxamide

N,O-dimethylhydroxylamine hydrochloride (1.089 g, 11.16 mmol) and triethylamine (3.92 ml, 27.9 mmol) were added to a solution of 5-fluoro-1H-indole-2-carboxylic acid (2.0 g, 11.16 mmol) in dichloromethane(30 mL) and stirred at room temperature for 5 min. Then 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.140 g, 11.16 mmol) was added and stirred for 20 hours. After reaction, solvent was removed. The residue was suspended in minimum volume of acetone and the insoluble white solid was removed by filtration. After being concentrated in vacuo, the mixture was poured into saturated sodium bicarbonate aqueous solution, and the aqueous phase was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (2:1) to give 690 mg (28% yield) of the title compound as a white crystal:

^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.6 (1H, s), 7.44 (1H, m), 7.38 (1H, d, J=2.6 Hz), 7.12 (1H, d, J=1.5 Hz), 7.06 (1H, dt, J=9.5, 2.6 Hz), 3.78 (3H, s), 3.32 (3H, s).

Step-2: 5-fluoro-1H-indole-2-carbaldehyde

Lithium aluminium hydride (0.094 g, 2.488 mmol) was added to a solution of 5-fluoro-N-methoxy-N-methyl-1H-indole-2-carboxamide (0.691 g, 3.11 mmol) in tetrahydrofuran (10 ml) at 0° C. and stirred for 1 hour. The reaction mixture was cooled to 0° C. and 25% ammonia solution was added dropwise to the reaction mixture until lithium aluminium hydride color turn gray to white. Then dichloromethane and cerite was added to the reaction mixture and stirred for 30 min. The mixture was filtered through a pad of Celite and concentrated in vacuo to give 523 mg of the crude title compound. This was used for the next step without further purification:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.85 (1H, s), 9.13 (1H, brs), 7.42-7.36 (2H, m), 7.24 (1H, d, J=1.1Hz), 7.16 (1H, dt, J=9.2, 2.6 Hz).

Step-3: 5-fluoro-1-tosyl-1H-indole-2-carbaldehyde

p-Toluenesulfonyl chloride (2.445 g, 12.82 mmol), N,N-dimethyl-4-aminopyridine (0.196 g, 1.603 mmol) and triethylamine (2.253 ml, 16.03 mmol) were added to a solution of 5-fluoro-1H-indole-2-carbaldehyde (0.523 g, 3.21 mmol) in dichloromethane (10 ml) and stirred at room temperature for 20 hours. After reaction, the mixture was poured into saturated sodium bicarbonate aqueous solution, and the aqueous phase was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10:1) to give 823 mg (81% yield) of the title compound as a white crystal:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.5 (1H, s), 8.20 (1H, dd, J=10.0, 4.2 Hz), 7.62 (2H, d, J=8.4 Hz), 7.40 (1H, s), 7.29-7.19 (4H, m), 2.34 (3H, s).

Step-4: ethyl(E)-3-(5-fluoro-1-tosyl-1H-indol-2-yl) acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 5-fluoro-1-tosyl-1H-indole-2-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, d, J=16.1Hz), 8.17 (1H, dd, J=9.2, 4.4 Hz), 7.59 (2H, d, J=8.4 Hz), 7.19-7.05 (4H, m), 6.90 (1H, s), 6.35 (1H, d, J=16.1Hz), 4.30 (2H, q, J=7.3 Hz), 2.33 (3H, s), 1.37 (3H, t, J=7.3 Hz).

Step-5: ethyl trans-2-(5-fluoro-1-tosyl-1H-indol-2-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(5-fluoro-1-tosyl-1H-indol-2-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, dd, J=8.8, 4.4 Hz), 7.69 (2H, d, J=8.1Hz), 7.21 (2H, d, J=8.1Hz), 7.07-6.98 (2H, m), 6.23 (1H, s), 4.23 (2H, m), 2.91 (1H, m), 2.35 (3H, s), 1.82 (1H, m), 1.62 (1H, m), 1.32 (3H, t, J=7.3 Hz), 1.28 (1H, m).

Step-6: trans-2-(5-fluoro-1H-indol-2-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(5-fluoro-1-tosyl-1H-indol-2-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) 11.1 (1H, s), 7.21 (1H, dd, J=8.8, 4.8 Hz), 7.10 (1H, dd, J=10.3, 2.6 Hz), 6.81 (1H, dt, J=8.8, 2.6 Hz), 6.18 (1H, d, J=1.8 Hz), 2.48 (1H, m), 1.87 (1H, m), 1.42 (2H, m), LCMS (Method A) m/z: M+1 obs 220.3, tR=2.64 min.

Carboxylic Acid Intermediate-14

trans-2-(4-fluoro-1H-indol-3-yl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(4-fluoro-1-tosyl-1H-indol-3-yl) acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 4-fluoro-1-tosyl-1H-indole-3-carbaldehyde.

^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.88-7.72 (5H, m), 7.32-7.20 (3H, m), 6.95 (1H, dd, J=8.2 & 10.9 Hz), 6.48 (1H, d, J=16.1Hz), 4.24 (2H, q, J=7.2 Hz), 2.35 (3H, s), 1.32 (3H, t, J=7.2 Hz).

Step-2: ethyl trans-2-(4-fluoro-1-tosyl-1H-indol-3-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(4-fluoro-1-tosyl-1H-indol-3-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.77-7.70 (3H, m), 7.6-7.3 (4H, m), 6.95-6.86 (1H, m), 4.18 (2H, q, J=7.3 Hz), 2.72-2.62 (1H, m), 2.36 (3H, s), 1.87-1.79 (1H, m), 1.65-1.55 (1H, m), 1.35-1.25 (1H, m), 1.29 (3H, t, J=7.3 Hz).

Step-3: trans-2-(4-fluoro-1H-indol-3-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(4-fluoro-1-tosyl-1H-indol-3-yl)cyclopropanecarboxylate LCMS (Method A) m/z: M−1 obs 218.3, tR=2.52 min.

Carboxylic Acid Intermediate-15

trans-2-(quinolin-2-yl)cyclopropanecarboxylic acid

Step-1: ethyl trans-2-(quinolin-2-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(quinolin-2-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.04 (1H, d, J=8.8 Hz), 7.93 (1H, d, J=8.1Hz), 7.75 (1H, d, J=8.1Hz), 7.65 (1H, t, J=8.1Hz), 7.46 (1H, t, J=8.1Hz), 7.33 (1H, d, J=8.8 Hz), 4.18 (2H, d, J=7.3 Hz), 2.80-2.73 (1H, m), 2.47-2.40 (1H, m), 1.82-1.75 (1H, m), 1.71-1.64 (1H, m), 1.29 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 242.2, tR=3.09 min.

Step-2: trans-2-(quinolin-2-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(quinolin-2-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.27 (1H, d, J=8.8 Hz), 7.94 (1H, d, J=8.0 Hz), 7.87 (1H, d, J=8.0 Hz), 7.70 (1H, t, J=8.0 Hz), 7.58 (1H, d, J=8.8 Hz), 7.52 (1H, t, J=8.0 Hz), 2.75 (1H, br), 2.20 (1H, br), 1.68-1.48 (2H, m) (a signal due to COON was not observed), LCMS (Method A) m/z: M−1 obs 212.2, tR=2.27 min.

Carboxylic Acid Intermediate-16

trans-2-(1H-indazol-3-yl)cyclopropanecarboxylic acid

Step-1: methyl(E)-3-(1-tosyl-1H-indazol-3-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-11 from methyl (E)-3-(1H-indazol-3-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, d, J=8.8 Hz), 7.93-7.84 (4H, m), 7.60 (1H, t, J=7.7 Hz), 7.41 (1H, t, J=7.7 Hz), 7.30-7.24 (2H, m), 6.87 (1H, d, J=16.8 Hz), 3.84 (3H, s), 2.37 (3H, s), LCMS (Method A) m/z: M+1 obs 357.2, tR=3.32 min.

Step-2: methyl trans-2-(1-tosyl-1H-indazol-3-yl) cyclopropanecarboxylate

Prepared as in Stepl of Carboxylic acid intermediate-6 from methyl (E)-3-(1-tosyl-1H-indazol-3-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, d, J=8.0 Hz), 7.79 (2H, d, J=8.0 Hz), 7.69 (1H, d, J=8.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.33 (1H, t, J=8.0 Hz), 7.22 (2H, d, J=8.0 Hz), 3.73 (3H, s), 2.80-2.70 (1H, m), 2.35 (3H, s), 2.33-2.27 (1H, m), 1.72-1.62 (2H, m), LCMS (Method A) m/z: M+1 obs 371.2, tR=3.25 min.

Step-3: trans-2-(1H-indazol-3-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from methyl trans-2-(1-tosyl-1H-indazol-3-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.75 (1H, br), 7.78 (1H, d, J=8.0 Hz), 7.46 (1H, d, J=8.0 Hz), 7.33 (1H, t, J=8.0 Hz), 7.09 (1H, t, J=8.0 Hz), 2.77-2.65 (1H, m), 2.08-2.00 (1H, m), 1.58-1.47 (2H, m), LCMS (Method A) m/z: M−1 obs 201.3, tR=2.29 min.

Carboxylic Acid Intermediate-17

trans-2-(quinolin-7-yl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(quinolin-7-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from quinoline-7-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.95 (1H, d, J=4.4 Hz), 8.20 (1H, s), 8.15 (1H, d, J=8.8 Hz), 7.87 (1H, d, J=16.1Hz), 7.83 (1H, d, J=8.8 Hz), 7.73 (1H, d, J=8.8 Hz), 7.42 (1H, dd, J=4.4 & 8.0 Hz), 6.62 (1h, d, J=16.1Hz), 4.31 (2H, q, J=7.3 Hz), 1.37 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 228.3, tR=2.82 min.

Step-2: ethyl trans-2-(quinolin-7-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(quinolin-7-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) 8*8.91-8.85 (1H, m), 8.11 (1H, d, J=8.8 Hz), 7.80 (1H, s), 7.74 (1H, d, J=8.8 Hz), 7.40-7.30 (2H, m), 4.19 (2H, q, J=8.0 Hz), 2.76-2.67 (1H, m), 2.10-2.02 (1H, m), 1.76-1.68 (1H, m), 1.54-1.45 (1H, m), 1.30 (3H, t, J=8.0 Hz), LCMS (Method A) m/z: M+1 obs 242.3, tR=2.79 min.

Step-3: trans-2-(quinolin-7-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(quinolin-7-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.86 (1H, d, J=4.4 Hz), 8.31 (1H, d, J=8.8 Hz), 7.90 (1H, d, J=9.5 Hz), 7.81 (1H, s), 7.46 (1H, dd, J=4.4 & 8.8 Hz), 7.40 (1H, d, J=9.5 Hz), 2.66-2.58 (1H, m), 2.03-1.95 (1H, m), 1.57-1.50 (2H, m) (a signal due to COOH was not observed), LCMS (Method A) m/z: M−1 obs 212.3, tR=2.13 min.

Carboxylic Acid Intermediate-18

trans-2-(1-methyl-1H-indol-6-yl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(1-methyl-1H-indol-6-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 1-methyl-1H-indole-6-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, d, J=15.4 Hz), 7.60 (1H, d, J=8.0 Hz), 7.47 (1H, s), 7.34 (1H, d, J=8.0 Hz), 7.13 (1H, d, J=2.9 Hz), 6.49 (1H, d, J=2.9 Hz), 6.47 (1H, d, J=15.4 Hz), 4.27 (2H, q, J=7.3 Hz), 3.82 (3H, s), 1.35 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 230.3, tR=3.15 min.

Step-2: ethyl trans-2-(1-methyl-1H-indol-6-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(1-methyl-1H-indol-6-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, J=8.1Hz), 7.08 (1H, s), 7.00 (1H, d, J=2.9 Hz), 6.86 (1H, d, J=8.1Hz), 6.43 (1H, d, J=2.9 Hz), 4.18 (2H, q, J=7.4 Hz), 3.76 (3H, s), 2.72-2.63 (1H, m), 1.99-1.90 (1H, m), 1.66-1.59 (1H, m), 1.44-1.35 (1H, m), 1.29 (3H, t, J=7.4 Hz), LCMS (Method A) m/z: M+1 obs 244.3, tR=3.17 min.

Step-3: trans-2-(1-methyl-1H-indol-6-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(1-methyl-1H-indol-6-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ12.2 (1H, br), 7.42 (1H, d, J=8.1Hz), 7.26-7.20 (2H, m), 6.82 (1H, d, J=8.0 Hz), 6.35 (1H, d, J=2.9 Hz), 3.75 (3H, s), 2.50-2.44 (1H, m), 1.85-1.77 (1H, m), 1.47-1.38 (2H, m), LCMS (Method A) m/z: M−1 obs 214.2, tR=2.67 min.

Carboxylic Acid Intermediate-19

trans-2-(6-fluoro-1H-indol-3-yl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(6-fluoro-1-tosyl-1H-indol-3-yl) acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 6-fluoro-1-tosyl-1H-indole-3-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82-7.70 (6H, m), 7.34-7.25 (2H, m), 7.08 (1H, t, J=8.8 Hz), 6.48 (1H, d, J=16.1Hz), 4.27 (2H, q, J=7.3 Hz), 2.38 (3H, s), 1.34 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 388.2, tR=3.57 min.

Step-2: ethyl trans-2-(6-fluoro-1-tosyl-1H-indol-3-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(6-fluoro-1-tosyl-1H-indol-3-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (2H, d, J=8.0 Hz), 7.68 (1H, dd, J=2.2 & 9.5 Hz), 7.47 (1H, dd, J=5.1 & 8.8 Hz), 7.28-7.22 (2H, m), 7.00 (1H, dt, J=2.2 & 8.8 Hz), 4.19 (2H, q, J=7.3 Hz), 2.50-2.40 (1H, m), 2.36 (3H, s), 1.87-1.80 (1H, m), 1.61-1.53 (1H, m), 1.31 (3H, t, J=7.3 Hz), 1.28-1.21 (1H, m), LCMS (Method A) m/z: M+1 obs 402.2, tR=3.48 min.

Step-3: trans-2-(6-fluoro-1H-indol-3-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(6-fluoro-1-tosyl-1H-indol-3-yl)cyclopropanecarboxylate.

LCMS (Method A) m/z: M−1 obs 218.3, tR=2.54 min.

Carboxylic Acid Intermediate-20

trans-2-((4-chlorophenoxy)methyl)cyclopropanecarboxylic acid

Step-1: ethyl trans-2-((4-chlorophenoxy)methyl) cyclopropanecarboxylate

To a suspension of sodium hydride (60%, 650 mg, 16.3 mmol) in toluene (25 mL) was added dropwise a solution of triethyl phosphonoacetate (3.64 g, 16.3 mmol) in toluene (5 mL) at 0° C. After stirring at room temprtature for 10 min, 2-((4-chlorophenoxy)methyl)oxirane (1.50 g, 8.1 mmol) was added, and the mixture was refluxed with stirring for 1 day. After cooling to room temperature, the mixture was poured into brine, and the aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10:1-5:1) to give 1.25 g (60%) of the title compound as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22 (2H, d, J=8.8 Hz), 6.80 (2H, d, J=8.8 Hz), 4.15 (2H, q, J=7.3 Hz), 3.92 (1H, dd, J=6.6 & 10.2 Hz), 3.83 (1H, dd, J=6.6 & 10.2 Hz), 1.93-1.82 (1H, m), 1.71-1.65 (1H, m), 1.27 (3H, t, J=7.3 Hz), 1.01-0.93 (1H, m), 0.90-0.76 (1H, m), LCMS (Method A) m/z: M+1 obs 255.2, tR=3.25 min.

Step-2: trans-2-((4-chlorophenoxy)methyl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from trans-2-((4-chlorophenoxy)methyl)cyclopropanecarboxylic acid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22 (2H, d, J=8.8 Hz), 6.80 (2H, d, J=8.8 Hz), 3.96 (1H, dd, J=5.9 & 10.3 Hz), 8.81 (1H, dd, J=6.6 & 10.3 Hz), 2.00-1.90 (1H, m), 1.75-1.68 (1H, m), 1.41-1.32 (1H, m), 1.12-1.05 (1H, m) (a signal due to COOH was not observed), LCMS (Method A) m/z: M−1 obs 225.2, tR=2.80 min.

Carboxylic Acid Intermediate-21

trans-2-(isoquinolin-3-yl)cyclopropanecarboxylic acid

Step-1: ethyl (E)-3-(isoquinolin-3-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from isoquinoline-3-carbaldehyde.

^{1}H-NMR (300 MHz, $CDC1_3$) δ 9.25 (1H, s), 7.99 (1H, d, J=8.0 Hz), 7.85 (1H, d, J=7.3 Hz), 7.83 (1H, d, J=15. 4 Hz), 7.75-7.62 (3H, m), 7.19 (1H, d, J=15.4 Hz), 4.29 (2H, q, J=6.6 Hz), 1.35 (3H, t, J=6.6Hz), LCMS (Method A) m/z: M+1 obs 228.2, tR=2.99 min.

Step-2: ethyl trans-2-(isoquinolin-3-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(isoquinolin-3-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.11 (1H, s), 7.92 (1H, d, J=8.0 Hz), 7.75 (1H, d, J=7.4 Hz), 7.66 (1H, m), 7.58 (1H, s), 7.53 (1H, m), 4.19 (2H, q, J=6.6 Hz), 2.76 (1H, m), 2.33 (1H, m), 1.77-1.63 (2H, m), 1.29 (3H, t, J=6.6 Hz).

Step-3: trans-2-(isoquinolin-3-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(isoquinolin-3-yl)cyclopropanecarboxylate.

LCMS (Method A) m/z: M+1 obs 214.3, tR=2.40 min.

Carboxylic Acid Intermediate-22

trans-2-(quinolin-3-yl)cyclopropanecarboxylic acid

Step-1: ethyl trans-2-(quinolin-3-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(quinolin-3-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.77 (1H, d, J=2.2 Hz), 8.08 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=2.2 Hz), 7.75 (1H, dd, J=8.0, 1.5 Hz), 7.68 (1H, td, J=6.6, 1.5 Hz), 7.54 (1H, m), 4.22 (2H, q, J=7.3 Hz), 2.73 (1H, m), 2.07 (1H, m), 1.75 (1H, m), 1.46 (1H, m), 1.31 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 242.3, tR=2.85 min.

Step-2: trans-2-(quinolin-3-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(quinolin-3-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.83 (1H, d, J=2.2 Hz), 8.10 (1H, d, J=2.2 Hz), 7.99 (1H, d, J=8.0 Hz), 7.89 (1H, d, J=7.3 Hz), 7.71 (1H, m), 7.59 (1H, t, J=8.1Hz), 2.63 (1H, m), 2.05 (1H, m), 1.55 (2H, t, J=6.6 Hz), LCMS (Method A) m/z: M+1 obs 214.3, tR=2.30 min.

Carboxylic Acid Intermediate-23

2-(3-(difluoromethoxy)phenyl)cyclopropanecarboxylic acid

Step-1: ethyl(E)-3-(3-(difluoromethoxy)phenyl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 3-(difluoromethoxy)benzaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, d, J=16.1Hz), 7.62 (1H, dd, J=7.7, 1.8 Hz), 7.38 (1H, dt, J=7.7, 1.5 Hz), 7.26-7.16 (2H, m), 6.56 (1H, t, J=73 Hz), 6.48 (1H, d, J=16.1Hz), 4.27 (2H, q, J=7.0 Hz), 1.34 (3H, t, J=7.0 Hz).

Step-2: ethyl trans-2-(3-(difluoromethoxy)phenyl) cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(3-(difluoromethoxy)phenyl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25-7.09 (3H, m), 6.97 (1H, dd, J=7.7, 1.8 Hz), 6.52 (1H, t, J=74 Hz), 4.19 (2H, m), 2.71 (1H, m), 1.83 (1H, m), 1.61 (1H, m), 1.31 (1H, m), 1.28 (3H, t, J=7.0 Hz).

Step-3: trans-2-(3-(difluoromethoxy)phenyl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(3-(difluoromethoxy)phenyl)cyclopropanecarboxylate.

LCMS (Method A) m/z: M−1 obs 228.2, tR=2.66 min.

Carboxylic Acid Intermediate-24

trans-2-(2-fluoro-5-methoxyphenyl)cyclopropanecarboxylic acid

Step-1: ethyl trans-2-(2-fluoro-5-methoxyphenyl) cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(2-fluoro-5-methoxyphenyl)acrylate.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.93 (1H, t, J=9.2 Hz), 6.66 (1H, dt, J=8.9, 3.3 Hz), 6.45 (1H, dd, J=5.9, 3.0 Hz), 4.17 (2H, q, J=7.3 Hz), 3.75 (3H, s), 2.62 (1H, m), 1.93 (1H, m), 1.58 (1H, m), 1.33 (1H, m), 1.28 (3H, t, J=7.3 Hz).

Step-2: trans-2-(2-fluoro-5-methoxyphenyl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(2-fluoro-5-methoxyphenyl)cyclopropanecarboxylate.

LCMS (Method A) m/z: M−1 obs 209.2, tR=2.59 min.

Carboxylic Acid Intermediate-25

trans-2-((1H-indol-1-yl)methyl)cyclopropanecarboxylic acid

Step-1: ethyl trans-2-((1H-indol-1-yl)methyl)cyclopropanecarboxylate

To a suspension of sodium hydride (60%, 55 mg, 1.4 mmol) in DMF (5 mL) was added indole (135 mg, 1.2 mmol). After stirring at room temperature for 10 min, ethyl 2-(((me-

thylsulfonyl)oxy)methyl)cyclopropanecarboxylate (307 mg, 1.4 mmol) was added. After stirring at room temperature for 6 h, the mixture was poured into water, and the aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10:1-5:1) to give 153 mg (54%) of the title compound as a pale brown oil;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67-7.60 (1H, m), 7.42-7.09 (4H, m), 6.57-6.50 (1H, m), 4.22-4.02 (4H, m), 1.96-1.86 (1H, m), 1.69-1.62 (1H, m), 1.31-1.25 (1H, m), 1.24 (3H, t, J=7.3 Hz), 0.95-0.87 (1H, m), LCMS (Method A) m/z: M+1 obs 244.3, tR=3.17 min.

Step-2: trans-2-((1H-indol-1-yl)methyl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-((1H-indol-1-yl)methyl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66-7.61 (1H, m), 7.43-7.08 (4H, m), 6.58-6.50 (1H, m), 4.20-4.06 (2H, m), 2.00-1.91 (1H, m), 1.70-1.62 (1H, m), 1.36-1.27 (1H, m), 1.01-0.94 (1H, m) (a signal due to COOH was not observed), LCMS (Method A) m/z: M−1 obs 214.3, tR=2.72 min.

Carboxylic Acid Intermediate-26

trans-2-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)cyclopropanecarboxylic acid

Step-1:1-((3-methyloxetan-3-yl)methyl)-1H-indole-6-carbaldehyde

Prepared as in Step-1 of Carboxylic acid intermediate-11 from 1H-indole-6-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ10.06 (1H, s), 7.93 (1H, s), 7.73 (1H, d, J=8.0 Hz), 7.64 (1H, d, J=8.0 Hz), 7.30 (1H, d, J=3.7 Hz), 6.63 (1H, d, J=3.7 Hz), 4.67 (2H, d, J=6.6 Hz), 4.45 (2H, s), 4.42 (2H, d, J=6.6 Hz), 1.31 (3H, s), LCMS (Method A) m/z: M+1 obs 230.2, tR=2.62 min.

Step-2: ethyl(E)-3-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 1-((3-methyloxetan-3-yl)methyl)-1H-indole-6-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (1H, d, J=16.1Hz), 7.62 (1H, d, J=8.1Hz), 7.50 (1H, s), 7.36 (1H, d, J=8.1Hz), 7.15 (1H, d, J=3.0 Hz), 6.55 (1H, d, J=3.0 Hz), 6.47 (1H, d, J=16.1Hz), 4.68 (2H, d, J=5.9 Hz), 4.43 (2H, d, J=5.9 Hz), 4.40 (2H, s), 4.29 (2H, q, J=7.4 Hz), 1.36 (3H, t, J=7.4 Hz), 1.32 (3H, s), LCMS (Method A) m/z: M+1 obs 300.2, tR=3.09 min.

Step-3: ethyl trans-2-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from ethyl (E)-3-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, J=8.1Hz), 7.13 (1H, s), 7.01 (1H, d, J=2.9 Hz), 6.83 (1H, d, J=8.1Hz), 6.48 (1H, d, J=3.0 Hz), 4.67 (2H, d, J=6.6 Hz), 4.41 (2H, d, J=6.6 Hz), 4.34 (2H, s), 4.18 (2H, q, J=7.3 Hz), 2.67 (1H, m), 1.93 (1H, m), 1.63 (1H, m), 1.40-1.25 (7H, m), LCMS (Method A) m/z: M+1 obs 314.2, tR=3.10 min.

Step-4: trans-2-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, d, J=8.1Hz), 7.17 (1H, s), 7.03 (1H, d, J=3.7 Hz), 6.85 (1H, d, J=8.1Hz), 6.50 (1H, d, J=3.6 Hz), 4.69 (2H, d, J=6.6 Hz), 4.43 (2H, d, J=5.9 Hz), 4.35 (2H, s), 2.76 (1H, m), 1.96 (1H, m), 1.72 (1H, m), 1.49 (1H, m), 1.32 (3H, s).

Carboxylic Acid Intermediate-27

trans-2-(2-(isopropylamino)pyridin-4-yl)cyclopropanecarboxylic acid

Step-1: ethyl trans-2-(2-chloropyridin-4-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(2-chloropyridin-4-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, d, J=5.1Hz), 7.04 (1H, s), 6.91 (1H, dd, J=5.1, 1.4 Hz), 4.18 (2H, q, J=6.6 Hz), 2.46 (1H, m), 2.00 (1H, m), 1.71 (1H, m), 1.36 (1H, m), 1.29 (3H, t, 6.6 Hz), LCMS (Method A) m/z: M+1 obs 226.2, tR=2.82 min.

Step-2: ethyl trans-2-(2-(isopropylamino)pyridin-4-yl)cyclopropanecarboxylate

To a dioxane (5 mL) solution of ethyl trans-2-(2-chloropyridin-4-yl)cyclopropanecarboxylate (250 mg, 1.1 mmol) and isopropylamine (393 mg, 6.7 mmol) were added cesium carbonate (1.1 g, 3.3 mmol), Xantophos (224 mg, 0.4 mmol) and palladium acetate (50 mg, 0.2 mmol) at room temperature respectively. The mixture was sealed and stirred at 100 ° C. for 14 hours. After being filtered off, the filtrate was concentrated under reduced pressure, the residue was applied to a silica gel chromatography column and eluted with a hexane/ethyl acetate =6/1 to furnish 100 mg (36% yield) of the title as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (1H, d, J=5.9 Hz), 6.18 (1H, d, J=5.9 Hz), 6.11 (1H, s), 4.32 (1H, brd, J=7.3 Hz), 4.16 (2H, q, J=7.3 Hz), 3.87 (1H, m), 2.36 (1H, m), 1.93 (1H, m), 1.60 (1H, m), 1.33-1.18 (10H, m), LCMS (Method A) m/z: M+1 obs 249.3, tR=2.04 min.

Step-3: trans-2-(2-(isopropylamino)pyridin-4-yl) cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl trans-2-(2-(isopropylamino)pyridin-4-yl)cyclopropanecarboxylate.

LCMS (Method A) m/z: M+1 obs 221.3, tR=0.82 min.

Carboxylic Acid Intermediate-28

2-(1H-indol-4-yl)cyclopropanecarboxylic acid

Step-1: ethyl 2-(1-tosyl-1H-indol-4-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(1-tosyl-1H-indol-4-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, d, J=8.8 Hz), 7.76 (2H, d, J=8.1Hz), 7.59 (1H, d, J=4.4 Hz), 7.26-7.19 (3H, m), 6.85-6.80 (2H, m), 4.19 (2H, q, J=6.6 Hz), 2.73 (1H, m), 2.34 (3H, s), 1.94 (1H, m), 1.64 (1H, m), 1.36 (1H, m), 1.29 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 384.2, tR=3.47 min.

Step-2: 2-(1H-indol-4-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(1-tosyl-1H-indol-4-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, brs), 7.33-7.24 (2H, m), 7.14 (1H, t, J=7.3 Hz), 6.80 (1H, d, J=7.3 Hz), 6.72 (1H, m), 2.98 (1H, m), 2.05 (1H, m), 1.75 (1H, m), 1.58 (1H, m), LCMS (Method A) m/z: M+1 obs 202.2, tR=2.38 min.

Carboxylic Acid Intermediate-29

2-(8-chloroquinolin-2-yl)cyclopropanecarboxylic acid

Step-1: (E)-ethyl 3-(8-chloroquinolin-2-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 8-chloroquinoline-2-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, d, J=8.8 Hz), 7.96 (1H, d, J=15.4 Hz), 7.88 (1H, dd, J=7.3, 1.4 Hz), 7.77 (1H, d, J=7.3 Hz), 7.69 (1H, d, J=8.8 Hz), 7.50 (1H, t, J=8.1Hz), 7.13 (1H, d, J=15.4 Hz), 4.34 (2H, q, J=6.6 Hz), 1.40 (3H, t, J=6.6 Hz), LCMS (Method A) m/z: M+1 obs 262.1, tR=3.24 min.

Step-2: ethyl 2-(8-chloroquinolin-2-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(8-chloroquinolin-2-yl)acrylate.

LCMS (Method A) m/z: M+1 obs 276.1, tR=3.40 min.

Step-3: 2-(8-chloroquinolin-2-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(8-chloroquinolin-2-yl)cyclopropanecarboxylate.

LCMS (Method A) m/z: M+1 obs 248.2, tR=2.82 min.

Carboxylic Acid Intermediate-30

2-(1-methyl-1H-indazol-6-yl)cyclopropanecarboxylic acid

Step-1: (E)-ethyl 3-(1-methyl-1H-indazol-6-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 1-methyl-1H-indazole-6-carbaldehyde.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.97 (1H, s), 7.82 (1H, d, J=16.1Hz), 7.71 (1H, d, J=8.2 Hz), 7.50 (1H, s), 7.35 (1H, dd, J=8.6, 1.0 Hz), 6.53 (1H, d, J=16.1Hz), 4.28 (2H, q, J=6.9 Hz), 4.09 (3H, s), 1.35 (3H, t, J=6.9 Hz), LCMS (Method A) m/z: M+1 obs 231.2, tR=2.88 min.

Step-2: ethyl 2-(1-methyl-1H-indazol-6-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(1-methyl-1H-indazol-6-yl)acrylate.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.91 (1H, s), 7.61 (1H, d, J=8.6 Hz), 7.13 (1H, s), 6.87 (1H, dd, J=8.6, 1.3 Hz), 4.18 (2H, q, J=7.3 Hz), 4.04 (3H, s), 2.67 (1H, m), 1.98 (1H, m), 1.66 (1H, m), 1.41 (1H, m), 1.29 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 245.3, tR=2.95 min.

Step-3: 2-(1-methyl-1H-indazol-6-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(1-methyl-1H-indazol-6-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.94 (1H, s), 7.62 (1H, d, J=8.1Hz), 7.42 (1H, s), 6.92 (1H, d, J=8.4 Hz), 3.98 (3H, s), 2.49 (1H, m), 1.90 (1H, m), 1.48-1.43 (2H, m), LCMS (Method A) m/z: M+1 obs 217.2, tR=2.37 min.

Carboxylic Acid Intermediate-31

2-(1H-indol-5-yl)cyclopropanecarboxylic acid

Step-1: (E)-ethyl 3-(1-tosyl-1H-indol-5-yl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 1-tosyl-1H-indole-5-carbaldehyde.

^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.98 (1H, d, J=8.6 Hz), 7.76 (2H, d, J=8.6 Hz), 7.74 (1H, d, J=15.8 Hz), 7.66 (1H, s), 7.58 (1H, d, J=3.9 Hz), 7.50 (1H, d, J=8.6 Hz), 7.23 (2H, d, J=8.6 Hz), 6.66 (1H, d, J=3.3 Hz), 6.41 (1H, d, J=15.8 Hz), 4.26 (2H, q, J=7.2 Hz), 2.34 (3H, s), 1.33 (3H, t, J=7.2 Hz), LCMS (Method A) m/z: M+1 obs 370.2, tR=3.45 min.

Step-2: ethyl 2-(1-tosyl-1H-indol-5-yl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(1-tosyl-1H-indol-5-yl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (1H, d, J=8.8 Hz), 7.74 (2H, d, J=8.1Hz), 7.53 (1H, d, J=3.7 Hz), 7.25 (1H, d, J=2.2 Hz), 7.21 (2H, d, J=8.1Hz), 7.05 (1H, dd, J=8.8, 2.2 Hz), 6.58 (1H, d, J=3.7 Hz), 4.18 (2H, q, J=7.3 Hz), 2.57 (1H, m), 2.34 (3H, s), 1.88 (1H, m), 1.61 (1H, m), 1.32 (1H, m), 1.27 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 384.3, tR=3.45 min.

Step-3: 2-(1H-indol-5-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(1-tosyl-1H-indol-5-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.2 (1H, brs), 11.1 (1H, s), 7.36-7.30 (3H, m), 6.92 (1H, d, J=8.1Hz), 6.39 (1H, s), 2.49 (1H, m), 1.77 (1H, m), 1.49-1.37 (2H, m).

Carboxylic Acid Intermediate-32

2-(3-(benzyloxy)phenyl)cyclopropanecarboxylic acid

Step-1: ethyl 2-(3-(benzyloxy)phenyl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(3-(benzyloxy)phenyl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44-7.32 (5H, m), 7.19 (1H, m), 6.81 (1H, m), 6.72-6.69 (2H, m), 5.04 (2H, s), 4.16 (2H, q, J=7.3 Hz), 2.48 (1H, m), 1.89 (1H, m), 1.58 (1H, m), 1.30 (1H, m), 1.27 (3H, t, J=7.3 Hz).

Step-2:
2-(3-(benzyloxy)phenyl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(3-(benzyloxy)phenyl)cyclopropanecarboxylate. LCMS (Method A) m/z: M−1 obs 267.2, tR=3.03 min.

Carboxylic Acid Intermediate-33

2-(2-chloro-4-fluorophenyl)cyclopropanecarboxylic acid

Step-1: (E)-ethyl 3-(2-chloro-4-fluorophenyl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 2-chloro-4-fluorobenzaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (1H, d, J=16.1Hz), 7.62 (1H, dd, J=8.8, 6.6 Hz), 7.18 (1H, dd, J=7.3, 1.5 Hz), 7.02 (1H, m), 6.38 (1H, d, J=16.1Hz), 4.28 (2H, q, J=7.3 Hz), 1.35 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M−1 obs 229.2, tR=3.22 min

Step-2: ethyl
2-(2-chloro-4-fluorophenyl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(2-chloro-4-fluorophenyl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.12 (1H, dd, J=8.8, 2.9 Hz), 6.99 (1H, m), 6.89 (1H, m), 4.20 (2H, q, J=7.3 Hz), 2.66 (1H, m), 1.77 (1H, m), 1.61 (1H, m), 1.29 (3H, t, J=7.3 Hz), 1.29 (1H, m), LCMS (Method A) m/z: M−1 obs 243.2, tR=3.27 min.

Step-3:
2-(2-chloro-4-fluorophenyl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(2-chloro-4-fluorophenyl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.44 (1H, d, J=8.8 Hz), 7.25-7.10 (2H, m), 2.48 (1H, m), 1.70 (1H, m), 1.45-1.35 (2H, m), LCMS (Method A) m/z: M−1 obs 213.2, tR=2.72 min.

Carboxylic Acid Intermediate-34

2-(2-fluoro-4-methoxyphenyl)cyclopropanecarboxylic acid

Step-1: ethyl 2-(2-fluoro-4-methoxyphenyl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(2-fluoro-4-methoxyphenyl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.90 (1H, t, J=6.6 Hz), 6.65-6.55 (2H, m), 4.17 (2H, q, J=7.3 Hz), 3.77 (3H, s), 2.57 (1H, m), 1.86 (1H, m), 1.54 (1H, m), 1.28 (3H, t, J=7.3 Hz), 1.28 (1H, m), LCMS (Method A) m/z: M+1 obs 239.3, tR=3.13 min.

Step-2:
2-(2-fluoro-4-methoxyphenyl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(2-fluoro-4-methoxyphenyl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.01 (1H, t, J=8.8 Hz), 6.79 1H, m), 6.69 (1H, m), 3.72 (3H, s), 2.34 (1H, m), 1.71 (1H, m), 1.40-1.30 (2H, m), LCMS (Method A) m/z: M−1 obs 209.2 tR=2.60 min.

Carboxylic Acid Intermediate-35

2-(2,4,6-trifluorophenyl)cyclopropanecarboxylic acid

Step-1: (E)-ethyl 3-(2,4,6-trifluorophenyl)acrylate

Prepared as in Step-1 of Carboxylic acid intermediate-7 from 2,4,6-trifluorobenzaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69 (1H, d, J=16.8 Hz), 6.77-6.65 (3H, m), 4.28 (2H, q, J=7.3 Hz), 1.35 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 231.2, tR=3.18 min.

Step-2: ethyl
2-(2,4,6-trifluorophenyl)cyclopropanecarboxylate

Prepared as in Step-1 of Carboxylic acid intermediate-6 from (E)-ethyl 3-(2,4,6-trifluorophenyl)acrylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.66-6.50 (2H, m), 4.18 (2H, q, J=7.3 Hz), 2.40 (1H, m), 2.07 (1H, m), 1.58-1.44 (2H, m), 1.30 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 245.2 tR=3.23 min.

Step-3:
2-(2,4,6-trifluorophenyl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(2,4,6-trifluorophenyl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.18-7.10 (2H, m), 2.17 (1H, m), 1.88 (1H, m), 1.45-1.30 (2H, m), LCMS (Method A) m/z: M−1 obs 215.2 tR=2.65 min.

Carboxylic Acid Intermediate-36

2-(5-cyano-1H-benzo[d]imidazol-2-yl)cyclopropanecarboxylic acid

Step-1: ethyl 2-(5-cyano-1H-benzo[d]imidazol-2-yl) cyclopropanecarboxylate

To a mixture of 3,4-diaminobenzonitrile (326 mg, 2.45 mmol), trans-2-(ethoxycarbonyl)cyclopropanecarboxylic acid (323 mg, 2.04 mmol), and triethylamine (1.44 mL, 10.2 mmol) in DMF (10 mL) was added HBTU (1.01 g, 2.66 mmol). After stirring at room temperature for 3 h, the mixture was poured into water, and the aqueous phase was extracted with EtOAc twice. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. To the residue was added acetic acid (10 mL), and the mixture was stirred at 90° C. for 12 h. After cooling to room temperature, the solvent was removed in vacuo. The residue was poured into saturated sodium bicarbonate aqueous solution, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica

gel eluting with hexane/ethyl acetate to give 210 mg (40%) of the title compound as a white amorphous:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.65 (1H, m), 7.73-7.68 (1H, m), 7.53-7.43 (2H, m), 4.20 (2H, q, J=7.3 Hz), 2.66-2.57 (1H, m), 2.51-2.41 (1H, m), 1.88-1.80 (1H, m), 1.80-1.70 (1H, m), 1.30 (3H, t, J=7.3 Hz), LCMS (Method A) m/z: M+1 obs 256.2, tR=2.61 min.

Step-2: 2-(5-cyano-1H-benzo[d]imidazol-2-yl)cyclopropanecarboxylic acid

Prepared as in Step-2 of Carboxylic acid intermediate-6 from ethyl 2-(5-cyano-1H-benzo[d]imidazol-2-yl)cyclopropanecarboxylate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (1H, s), 7.63 (1H, d, J=8.1Hz), 7.53 (1H, d, J=8.1Hz), 2.63-2.55 (1H, m), 2.20-2.12 (1H, m), 1.65-1.51 (2H, m) (signals due to NH and COOH were not observed), LCMS (Method A) m/z: M+1 obs 228.2, tR=1.88 min.

Carboxylic Acid Intermediate-37

4-((1H-imidazol-1-yl)methyl)-1H-indole-2-carboxylic acid

Step-1: Methyl 3-(2-methyl-6-nitrophenyl)propenoate

2-Bromo-3-nitrotoluene (0.5 g, 23 mmol), methyl acrylate (0.39 g, 46 mmol,), palladium acetate (29 mg, 1.3 mmol), triphenylphosphine (0.06 g, 0.23 mmol,) and TEA (0.4 mL) were combined in a sealed tube and heated to 95° C. for 24 h. The residue was dissolved in MeOH, the solvent was removed and the crude product was purified by column chromatography (EtOAc:hexane=7.5:92.5) to give 0.024 g (48% yield) of the title compound as a yellow oil:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, d, J=16.4 Hz), 7.75 (1H, d, J=8.0 Hz), 7.46 (1H, d, J=7.6 Hz), 7.35 (1H, q, J=8.0 Hz, 7.6 Hz), 3.79 (3H, s), 2.37 (3H, s).

Step-2: Methyl 4-methylindole-2-carboxylate

Methyl 3-(2-methyl-6-nitrophenyl)propenoate (0.24 g, 1.1 mmol) was dissolved in triethylphosphite (1 mL) and heated under reflux for 20 h. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (EtOAc:hexane=8:92) to give 0.15 g (71% yield) of the title compound as a pale yellow solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, br s), 7.25-7.18 (3H, m), 6.92 (1H, d, J=6.0 Hz), 3.93 (3H, s), 2.54 (3H, s).

Step-3: Methyl 1-tert-butoxycarbonyl-4-methylindole-2-carboxylate

Di-tert-butyl dicarbonate (0.35 g, 1.6 mmol,) and DMAP (0.015 g, 0.12 mmol) were added to a solution of Methyl 4-methylindole-2-carboxylate (0.15 g, 0.8 mmol) in acetonitrile (7.5 mL). The resulting mixture was stirred at room temperature for 16 h and the solvent evaporated in vacuo. The residue was portioned between ethyl acetate (7.5 mL) and water (7.5 mL). The aqueous layer was further extracted with ethyl acetate (2×7.5 mL) and the organic extracts combined, washed with saturated sodium bicarbonate, dried over sodium sulfate, evaporated in vacuo and purified by silica gel column (EtOAc:hexane=5:95) to give 0.13 g (59% yield) of the title compound as a pale yellow oil:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (1H, d, J=8.4 Hz), 7.31-7.03 (3H, m), 3.90 (3H, s), 2.50 (3H, s), 1.60 (9H, s).

Step-4: Methyl 4-bromomethyl-1-tert-butoxycarbonylindole-2-carboxylate

A solution of methyl 1-tert-butoxycarbonyl-4-methylindole-2-carboxylate (0.13 g, 0.48 mmol), NBS (0.087 g, 0.48 mmol), and AIBN (4 mg, 0.024 mmol) in carbon tetrachloride (1.9 mL) was heated to reflux for 3 h. The reaction mixture was cooled to room temperature and filtered and washed with carbon tetrachloride. The filtrate was evaporated to give a yellow oil that was purified by silica gel chromatography (EtOAc:hexane=8:92) to give 0.12 g (72% yield) of the title compound as a pale yellow solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, d, J=8.4 Hz), 7.38-7.27 (3H, m), 4.73 (2H, s), 3.94 (3H, s).

Step-5: 4-Imidazol-1-ylmethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methy ester

A solution of Methyl 4-bromomethyl-1-tert-butoxycarbonylindole-2-carboxylate (0.92 g, 2.4 mmol) and imodazole (0.82 g, 12 mmol) was stirred at 90° C. in acetonitrile (14 mL) for 5 h. The reaction mixture was cooled to room temperature and evaporated to dryness. The residue was purified by silica gel column chromatography (MeOH:DCM=8:92) to give 0.413 g (46% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (1H, d, J=8.4 Hz), 7.59 (1H, s), 7.39 (1H, q, J=7.6 Hz, 8.4 Hz), 7.08 (1H, s), 7.04 (1H, d, J=7.6 Hz), 6.94 (1H, s), 6.88 (1H, s), 5.33 (2H, s), 3.91 (3H, s), 1.62 (9H, s).

Step-6: 4-((1H-imidazol-1-yl)methyl)-1H-indole-2-carboxylic acid

The mixture of 4-Imidazol-1-ylmethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methy ester (350 mg, 0.99 mmol) and 2N aqueous sodium hydroxide solution (1 mL. 2 mmol) in THF (5 mL) was refluxed at 80° C. with stirring for 2 days. 2N hydrochloric acid was added until pH was 7.0. The mixture was concentrated in vacuo. The resulting percipitate was collected by filtration and washed with dichloromethane, methanol, H_2O and ethyl acetate to give 63 mg (27% yield) of the title compound as a white solid:

^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.82 (1H, s), 6.72 (1H, d, J=8.8 Hz), 6.65 (1H, s), 6.55 (1H, s), 6.50 (1H, t, J=7.3 Hz), 6.36 (1H, s), 6.29 (1H, d, J=6.6 Hz), 4.86 (2H, s).

Example 1

(R)-5-tert-butyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)isoxazole-3-carbox amide

To a suspension of (R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine 2HCl salt (18 mg, 0.06 mmol) and 5-tert-butylisoxazole-3-carboxylic acid (10 mg, 0.06 mmol) in dichloromethane (2 mL) were added triethylamine (19 mg, 0.18 mmol), EDC (19 mg, 0.1 mmol) and HOBT (9.4 mg, 0.06 mmol) respectively. The reaction mixture was stirred at room temperature for 18 hours. The solvent was evaporated by N_2-flow. The resulting residue was dissolved into ethyl acetate and water was added to the mixture. The organic layer was then washed with brine, and dried over sodium sulfate. After the filtration to separate solvent and sodium sulfate, the solvent was removed under reduced pressure to give the resi-

due. The residue was diluted with methanol and applied onto a strong cation exchange cartridge (BondElute(registered trademark) SCX, 1 g/6 mL, Varian Inc.), and the solid phase matrix was rinsed with methanol (6 mL). The crude mixture was eluted in a collection tube with 1 mol/L ammonia in methanol (6 mL) and concentrated in vacuo. The residue was purified by preparative LC-MS to give 17 mg, (75% yield) of the title compound.

By a method similar to Example 1 except that the reactant is different, the following compounds of Examples 2-27, 30-80, 82-241, 243-254, 258-291, 307-313, 315-423 and 426-464 were similarly prepared (also see Table 1). The reactants were used commercial available materials, otherwise noted in the intermediate parts.

Example 28

(R)-2-(4-bromophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamid e

To a suspension of (R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine 2HCl salt (173 mg, 0.79 mmol) and 2-(4-bromophenoxy)acetic acid (200 mg, 0.87 mmol) in dichloromethane (5 mL) were added triethylamine (400 mg, 3.9 mmol), EDC (180 mg, 0.94 mmol) and HOBT (60 mg, 0.39 mmol) respectively. The reaction mixture was stirred at room temperature for 18 hours. Sat. ammonia hydrochloride aqueous solution was added to the mixture. The organic layer was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After the filtration to separate solvent and sodium sulfate, the solvent was removed under reduced pressure to give the residue, which was applied to a silica gel chromatography column and eluted with a hexane/ethylacetate=2/1 (v/v) to furnish 276 mg (81% yield) of the title as a colorless oil;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, m), 7.66 (1H, brd, J=8.1Hz), 7.41 (2H, d, J=8.8 Hz), 7.26-7.24 (2H, m), 6.84 (2H, d, J=8.8 Hz), 5.22 (1H, m), 4.48 (2H, qAB, J=14.6 Hz), 4.40 (2H, qAB, J=8.1Hz), 1.49 (3H, d, J=7.3 Hz), LCMS (Method A) m/z: M+1 434.8; tR=3.15 min.

Example 29

(R)-2-(4-cyclopropylphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acet amide

To a solution of (R)-2-(4-bromophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide (100 mg, 0.23 mmol) and cyclopropylboronic acid (26 mg, 0.30 mmol) in dioxane (2 mL) were added 1.27 M potassium phosphate (0.36 mL) and tetrakistriphenyl phosphine palladium (13 mg, 0.012 mmol) at room temperature. The mixture was stirred at 120° C. using microwave oven for 2 hours. The mixture was dried over magnesium sulfate. After the filtration to separate solvent and magnesium sulfate, the solvent was removed under reduced pressure to give the residue. The residue was diluted with methanol and applied onto a strong cation exchange cartridge (BondElute(registered trademark) SCX, 1 g/6 mL, Varian Inc.), and the solid phase matrix was rinsed with methanol (6 mL). The crude mixture was eluted in a collection tube with 1 mol/L ammonia in methanol (6 mL) and concentrated in vacuo. The residue was purified by preparative LC-MS to give 6.5 mg, (7% yield) of the title compound.

Example 81

(R)-N-(1-(5-(pyridin-2-ylmethoxy)pyridin-2-yl) ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide

Step-1: (R)-N-(1-(5-hydroxypyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide

A mixture of (R)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide (Example 63, 550 mg, 1.3 mmol) and palladium hydroxide on carbon (20 wt. %, 50 mg) in methanol (30 mL) was hydrogenated for 6 hours. The mixture was filtered through a pad of celite, washed with methanol, the filtrate was concentrated gave 410 mg (94% yield) of (R)-N-(1-(5-hydroxypyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide as a white crystalline solid;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19 (1H, d, J=2.9 Hz), 7.77 (1H, d, J=7.3 Hz), 7.58 (2H, d, J=8.1Hz), 7.14 (1H, dd, J=8.8 Hz, 2.9 Hz), 7.08-7.02 (3H, m), 5.20-5.10 (1H, m), 4.58 (1H, d, J=13.9 Hz), 4.51 (1H, d, J=13.9 Hz), 1.48 (3H, d, J=6.6 Hz), LCMS (Method A) m/z: M+1 obs 341.

Step-2: (R)-N-(1-(5-(pyridin-2-ylmethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)a cetamide

A mixture of (R)-N-(1-(5-hydroxypyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide (30 mg, 0.088 mmol), 2-(bromomethyl)pyridine hydrobromide (22 mg, 0.088 mmol), and cesium carbonate (115 mg, 0.35 mmol) in DMF (3 mL) was heated at 90° C. overnight. After cooling, the mixture was filtered through a pad of celite, washed with dichloromethane, the filtrate was concentrated, and the residue was purified by SCX cartridge to give 34 mg (89% yield) of (R)-N-(1-(5-(pyridin-2-ylmethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)a cetamide as a clear colorless oil; LCMS (Method A) m/z: M+1 obs 432, M−1 obs 430

Alternated route for Mixture of Example 133 and 134 trans-2-(1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopr opanecarboxamide

Step-1: (R,E)-3-(1H-indol-3-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acrylamide

To a suspension of (R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine 2HCl salt (1.1 g, 3.8 mmol) and (E)-3-(1-(tert-butoxycarbonyl)-1H-indol-3-yDacrylic acid (1.0 g, 3.5 mmol) in dichloromethane (8 mL) were added triethylamine (1.8 g, 17 mmol), EDC (800 mg, 4.2 mmol) and HOBT (270 mg, 1.7 mmol) respectively. The reaction mixture was stirred at room temperature for 6 hours. Sat. sodium bicarbonate aqueous solution was added to the mixture. The organic layer was extracted with ethyl acetate, washed with brine, and dried over sodium sulfate. After the filtration to separate solvent and sodium sulfate, the solvent was removed under reduced pressure to give the residue, which was applied to a silica gel chromatography column and eluted with a hexane/ethylacetate=2/1 (v/v) to furnish 900 mg (53% yield) of the title as a yellow solid;

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, d, J=1.5 Hz), 8.18 (1H, d, J=8.0 Hz), 7.90-7.70 (3H, m), 7.40-7.20 (4H, m), 6.93 (1H, d, J=8.0 Hz), 6.59 (1H, d, J=16.1Hz), 5.30 (1H, m), 4.39 (2H, q, J=8.0 Hz), 1.08 (9H, s), 1.53 (3H, d, J=6.6 Hz), LCMS (Method A) m/z: M+1 490.3; tR=3.44 min.

Step-2: trans-2-(1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanec arboxamide

To a solution of (R,E)-3-(1H-indol-3-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acrylamide (600 mg, 1.3 mmol) in dichloromethane (10 mL) was added ethylzinc (4.1 mL, 4.1 mmol, 1.0 M) at room temperature. After being stirred at room temperature for 3 min, diiodomethane (1.8 g, 6.7 mmol) was added to the mixture. The mixture was refluxed at 55° C. with stirring for 18 hours. sat. ammonia hydrochloride aqueous solution was added to the mixture. The organic layer was extracted with ethyl acetate, washed with brine, dried over sodium sulfate. After the filtration to separate solvent and sodium sulfate, the solvent was removed under reduced pressure to give the residue, which was applied to a silica gel chromatography column and eluted with a hexane/ethylacetate=1/1 (v/v) and preparative LC-MS to give 14 mg, (3% yield) of the title compound as a white solid (2:1 mixture of the diastereomers).

^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.99 (1H, brs), 7.60 (1H, m), 7.34 (1H, m), 7.26-7.22 (2H, m), 7.18 (1H, m), 7.08 (1H, m), 6.95-6.86 (2H, m),5.21 (1H, m), 4.40 (2H, q, J=7.9 Hz), 2.54 (1H, m), 1.68 (1H, m), 1.60 (1H, m), 1.48 (3H, d, J=6.8 Hz), 1.29 (1H, m),LCMS (Method A) m/z: M+1 404.3; tR=2.98 min.

Example 242

(1S*,2S*)-2-(4-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethy

Dcyclopropanecarboxamide

A mixture of palladium hydroxide on carbon 20 wt % loading (63 mg) and (1S*,2S*)-2-(4-(benzyloxy)phenyl)-N-(R-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethy l)cyclopropanecarboxamide (631 mg, 1.341 mmol) in methanol (30 ml) was stirring for 4 hours at room temperature under H_2 atmosphere. The mixture was filtered through a pad of celite, washed with ethyl acetate, the filtrate was concentrated to give 485 mg (95% yield) of title compound as a white amorphous. 8 mg of the residue was purified by preparative LC-MS to give 4.8 mg of the title compound.

Example 255

(1S*,2S*)-2-(3-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethy l)cyclopropanecarboxamide

Prepared as in Example 242 from (1S*,2S*)-2-(3-(benzyloxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)et hyl)cyclopropanecarboxamide. The residue was purified by preparative LC-MS to give 5.4 mg of the title compound.

Example 256

(1S*,2S*)-2-(4-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide

Step-1: tert-butyl 2-(4-((1S*,2S*)-2-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)carbamoyl)cyclopropyl)phenoxy)acetate

A mixture of tert-butyl 2-bromoacetate (0.063 ml, 0.434 mmol), potassium carbonate (109 mg, 0.789 mmol) and (1S*,2S*)-2-(4-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide (150 mg, 0.394 mmol) in dichloromethane (4 ml) was refluxed with stirring for 3 hours. After cooling to room temperature, the mixture was poured into water, and the aqueous layer was extracted with ethyl acetate, dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from tetrahydrofuran/hexane. To give 137 mg (70% yield) of title compound as a white crystal:

^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.55 (1H, d, J=8.1Hz), 8.31 (1H, d, J=2.6 Hz), 7.49 (1H, dd, J=8.8, 2.9 Hz), 7.28 (1H, d, J=8.4 Hz), 7.03 (2H, d, J=8.4 Hz), 6.78 (2H, d, J=8.4 Hz), 4.95 (1H, t, J=7.3 Hz), 4.84 (2H, q, J=8.8 Hz), 4.59 (2H, s), 2.17 (1H, m), 1.89 (1H, m), 1.41 (9H, s), 1.32 (2H, d, J=6.6 Hz), 1.22 (1H, m), 1.09 (1H, m), LCMS (Method A) m/z: M+1 obs 495.1, tR=3.25 min.

Step-2: 2-(4-((1S*,2S*)-24(R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)carbamoyl)cyclopropyl) phenoxy)acetic acid

A mixture of trifluoroacetic acid (0.213 ml, 2.77 mmol) and tert-butyl 2-(4-((lS*,2S*)-2-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2- yl)ethyl)carbamoyl)cyclopropyl)phenoxy)acetate (137 mg, 0.277 mmol) in dichloromethane (5 ml) was refluxed with stirring for 6 hours. Excess trifluoroacetic acid and dichloromethane were removed under reduced pressure to give 200 mg of title compound as white solid. This was used next step without purification:

LCMS (Method A) m/z: M+1 obs 439.0, tR=2.54 min.

Step-3: (1S*,2S*)-2-(4-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethoxy)phenyl)-N-((R)-1-(5-(2,2, 2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide

A mixture of HBTU (28 mg, 0.075 mmol), triethylamine (0.03 mL, 0.25 mmol), 4,4-difluoropiperidine hydrochloride (9.5 mg, 0.060 mmol) and 2-(4-((1S*,2S*)-2-(((R)-1-(5-(2, 2,2-trifluoroethoxy)pyridin-2-yl)ethyl)carbamoyl)cycl opropyl)phenoxy)acetic acid (28 mg, 0.050 mmol) was stirring for 4 hours at room temperature. The mixture was poured into 2 mol/l hydrochloric acid, and the aqueous layer was extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The residue was purified by preparative LC-MS to give 13.7 mg (50% yield) of the title compound.

Example 257

(1S*,2S*)-2-(3-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide

Step-1: tert-butyl 2-(3-((1S*,2S*)-2-(((R)-1-(5-(2,2, 2-trifluoroethoxy)pyridin-2-yl)ethyl)carbamoyl)cyclopropyl)phenoxy)acetate

Prepared as in Step-1 of Example 256 from (1S*,2S*)-2-(3-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.56 (1H, d, J=7.7 Hz), 8.31 (1H, d, J=2.9 Hz), 7.49 (1H, dd, J=8.4, 2.9 Hz), 7.29 (1H, d, J=8.8 Hz), 7.16 (1H, t, J=7.7 Hz), 6.72-6.65 (3H, m), 4.95 (1H, t, J=7.3 Hz), 4.84 (2H, q, J=8.8 Hz), 4.61 (2H, s), 2.19 (1H, m), 1.98 (1H, m), 1.41 (9H, s), 1.32 (2H, d, J=7.0 Hz), 1.25 (1H, m), 1.15 (1H, m), LCMS (Method A) m/z: M+1 obs 495.1, tR=3.28 min.

Step-2: 2-(3-((1S*,2S*)-2-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)carbamoyl)cycl opropyl) phenoxy)acetic acid

Prepared as in Step-2 of Example 256 from tert-butyl 2-(3-((1S*,2S*)-2-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)carbamoyl)cycl opropyl)phenoxy)acetate.
LCMS (Method A) m/z: M+1 obs 439.0, tR=2.61 min.

Step-3: (1S*,2S*)-2-(3-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethoxy)phenyl)-N-((R)-1-(5-(2,2, 2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide

Prepared as in Step-3 of Example 256 from 2-(3-((1S*, 2S*)-2-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl) carbamoyl)cycl opropyl)phenoxy)acetic acid. The residue was purified by preparative LC-MS to give 11.4 mg of the title compound.

Example 292

(R)-4-(tert-butyl)-N-(1-(5-hydroxypyridin-2-yl) ethyl)benzamide

Prepared as in Example 242 from (R)-N-(1-(5-(benzyloxy) pyridin-2-yl)ethyl)-4-(tert-butyl)benzamide (Example 313).
^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.74 (1H, s), 8.60 (1H, d, J=8.1Hz), 8.04 (1H, d, J=2.9 Hz), 7.81 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.1Hz), 7.19 (1H, d, J=8.4 Hz), 7.10 (1H, dd, J=8.4, 2.9 Hz), 5.11 (1H, quintet, J=7.0 Hz), 1.43 (3H, d, J=7.0 Hz), 1.28 (9H, s), LCMS (Method A) m/z: M+1 obs 299.2, tR=3.21 min.

Example 293

(1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide

Step-1: (1R*,2R*)-2-(hydroxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)c yclopropanecarboxamide and (1S*,2S*)-2-(hydroxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)cy clopropanecarboxamide

To a mixture of (R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethanamine dihydrochloride (997 mg, 3.40 mmol), trans-2-(hydroxymethyl)cyclopropanecarboxylic acid (329 mg, 2.83 mmol), and triethylamine (1.99 mL, 14.2 mmol) in acetonitrile was added HBTU. After stirring at room temperature for 5 h, the mixture was poured into water, and the aqueous layer was extracted with dichloromethane three times. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with dichloromethane/methanol (20:1) to give 263 mg (29%) of upper spot (tentatively assigned as (1R*,2R*)-2-(hydroxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)c yclopropanecarboxamide) as a colorless oil and 292 mg of lower spot (tentatively assigned as (1S*,2S*)-2-(hydroxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)cy clopropanecarboxamide) as a crystal. (1R*,2R*)-2-(Hydroxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)cyclopropa necarboxamide: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.26 (1H, s), 7.27-7.21 (2H, m), 6.91 (1H, d, J=7.3 Hz), 5.11 (quintet, J=6.6 Hz), 3.66 (1H, dd, J=5.9 & 11.0 Hz), 3.41 (1H, dd, J=7.3 & 11.0 Hz), 1.70-1.60 (2H, m), 1.45 (3H, d, J=6.6 Hz), 1.27-1.19 (1H, m), 0.81-0.73 (1H, m) (a signal due to OH was not observed), LCMS (Method A) m/z: M+1 obs 319.1, tR=2.40 min. (1S*,2S*)-2-(Hydroxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropa necarboxamide: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.29 (1H, s), 7.27-7.20 (2H, m), 6.89 (1H, d, J=6.6 Hz), 5.11 (1H, quintet, J=6.6 Hz), 4.40 (2H, q, J=8.0 Hz), 3.66 (1H, dd, J=5.9 & 11.7 Hz), 3.49 (1H, dd, J=6.6 & 11.7 Hz), 1.77-1.65 (2H, m), 1.20-1.12 (1H, m), 0.77-0.70 (1H, m) (a signal due to OH was not observed), LCMS (Method A) m/z: M+1 obs 319.1, tR=2.37 min.

Step-2: (1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cy clopropanecarboxamide

To a mixture of (1S*,2S*)-2-(hydroxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cy clopropanecarboxamide (30 mg, 0.094 mmol) and phenol (16.0 mg, 0.17 mmol) in tetrahydrofuran (1 mL), triphenylphosphine (45 mg, 0.17 mmol) and di-tert-butyl azodicarboxylate (28.2 mg, 0.12 mmol) were added successively. After stirring at room temperature for 1 day, the mixture was poured into water, and the aqueous layer was extracted with dichloromethane three times. The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was purified by preparative LC-MS to give 12.1 mg (33% yield) of the title compound.

By a method similar to Example 293 except that the reactant is different, the following compounds of Examples 294-302 were similarly prepared (also see Table 3). The reactants were used commercially available materials, otherwise noted in the intermediate parts.

Example 303

(1S*,2S*)-2-(3-((3-methyloxetan-3-yl)methoxy) phenyl)-N-((R)-1-(5-(2,2,2-trifluoroe thoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide

A mixture of (1S*,2S*)-2-(3-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide (15 mg, 0.039 mmol), 3-(Chloromethyl)-3-methyloxetane (24 mg, 0.197 mmol) and potassium carbonate (27 mg, 0.197 mmol) in DMF (2 mL) was heated at 70° C. with stirring for 15 hours. The mixture was poured into water, and the aqueous layer was extracted with ethyl acetate, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative LC-MS to give 8.9 mg (49% yield) of the title compound.

Example 304

(1S*,2S*)-2-(44(3-methyloxetan-3-yl)methoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroe thoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide

Prepared as in Example 303 from (1S*,2S*)-2-(4-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)cyclopropanecarboxamide. The residue was purified by preparative LC-MS to give 8 mg of the title compound.

Example 305

(1S*,2S*)-2-(4-(pyridin-2-ylmethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyr idin-2-yl)ethyl) cyclopropanecarboxamide

A mixture of (1S*,2S*)-2-(4-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropan-

ecarboxamide (15 mg, 0.039 mmol), 2-(Bromomethyl)pyridine hydrobromide (100 mg, 0.394 mmol) and potassium carbonate (27 mg, 0.197 mmol) in DMF (2 mL) was heated at 70 oC with stirring for 2 days. The mixture was poured into water, and the aqueous layer was extracted with ethyl acetate, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative LC-MS to give 5 mg (27% yield) of the title compound.

Example 306

(1S*,2S*)-2-(3-(pyridin-2-ylmethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyr idin-2-yl)ethyl) cyclopropanecarboxamide

Prepared as in Example 305 from (1S*,2S*)-2-(3-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl) ethyl)cyclopropanecarboxamide. The residue was purified by preparative LC-MS to give 12 mg of the title compound.

Example 314

(R)-4-tert-butyl-N-(1-(5-(pyridin-2-ylmethoxy)pyridin-2-yl)ethyl)benzamide

Prepared as in Example 81 and Example 305 from (R)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-4-tert-butylbenzamide (Example 313).

Example 424

(R)-6-fluoro-N,1-dimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-ind ole-2-carboxamide

To a stirred solution of (R)-6-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxami de (Example 48, 18 mg, 0.046 mmol) in DMF (1 mL) was added sodium hydride (60%, 1.6 mg, 0.068 mmol) at room temperature. After 20 min, Iodomethane (0.0034 mL, 0.055 mmol) was added and the mixture was stirred at room temperature for 1 hour. The mixture was poured into water, and extracted with ethyl acetate, dried over sodium sulfate and concentrated under reduced pressure. The residue was diluted with methanol and applied onto a strong cation exchange cartridge (BondElute(registered trademark) SCX, 1 g/6 mL, Varian Inc.), and the solid phase matrix was rinsed with methanol (6 mL). The crude mixture was eluted in a collection tube with 1 mol/L ammonia in methanol (6 mL) and concentrated in vacuo. The residue was purified by preparative LC-MS to give 9.4 mg (50% yield) of the title compound

Example 425

(1S*,2S*)-N-methyl-2-(quinolin-2-yl)-N-((12)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide

Step-1: (1S*,2S*)-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide

Prepared as in Example 1 from 2-(quinolin-2-yl)cyclopropanecarboxylic acid (purified by chiral HPLC).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, s), 8.07 (1H, s), 8.00 (1H, d, J=8.0 Hz), 7.90 (1H, d, J=8.0 Hz), 7.74 (1H, d, J=8.0 Hz), 7.65 (1H, t, J=8.0 Hz), 7.45 (1H, t, J=8.0 Hz), 7.31 (1H, d, J=8.0 Hz), 6.58 (1H, d, J=8.0 Hz), 5.27 (1H, quintet, J=7.3 Hz), 4.80-4.67 (2H, m), 2.73-2.66 (1H, m), 2.35-2.27 (1H, m), 1.73-1.66 (2H, m), 1.50 (3H, d, J=7.3 Hz).

Step-2: (1S*,2S*)-N-methyl-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl) cyclopropanecarboxamide

Prepared as in Example 424 from (1S*,2S*)-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl) cyclopropanecarboxamide. The residue was purified by preparative LC-MS to give 11 mg of the title compound.

Example 426

(1R*,2R*)-N-methyl-2-(quinolin-2-yl)-N-((12)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide

Prepared as in Example 424 from (1R*,2R*)-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl) cyclopropanecarboxamide (Example 222). The residue was purified by preparative LC-MS to give 2.3 mg of the title compound.

Quality control analytical condition (Method B), the amine/carboxylic acid used, the purification method, and spectra data are described below for Examples 1-464 in Table 3 and Table 4.

TABLE 3

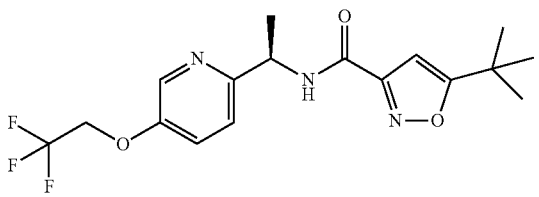
Example	Name	STRUCTURE
Example 1	(R)-5-tert-butyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)isoxazole-3-carboxamide	

TABLE 3-continued

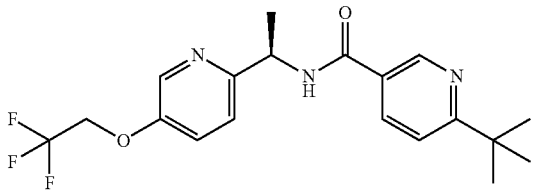
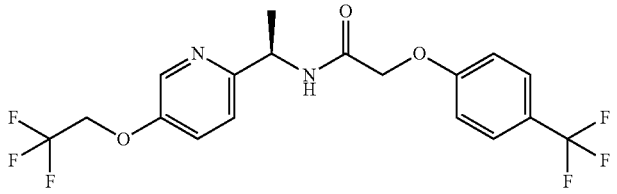
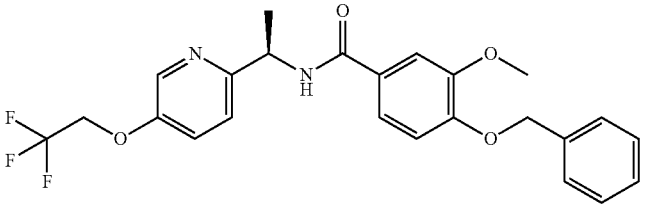
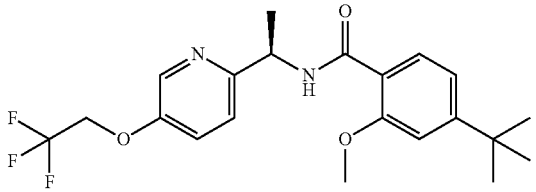
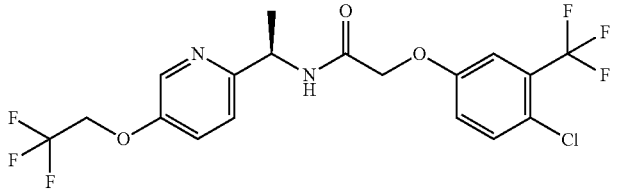
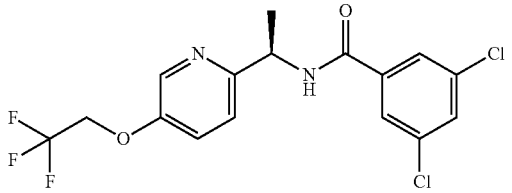
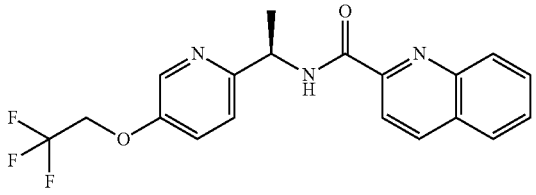
Example 2	(R)-6-tert-butyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)nicotinamide	
Example 3	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl) phenoxy)acetamide	
Example 4	(R)-4-(benzyloxy)-3-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 5	(R)-4-tert-butyl-2-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 6	(R)-2-(4-chloro-3-(trifluoromethyl)phenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 7	(R)-3,5-dichloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 8	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)quinoline-2-carboxamide	

TABLE 3-continued

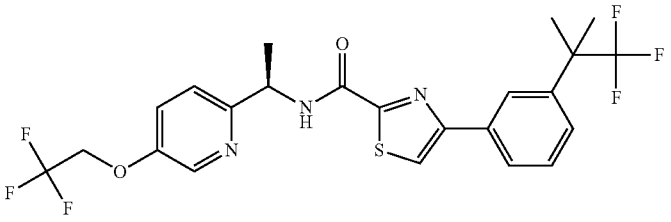
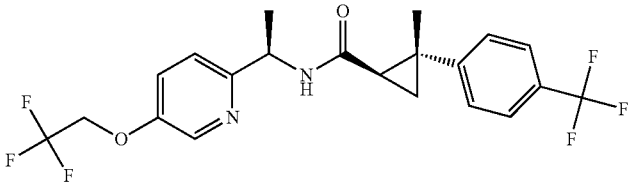
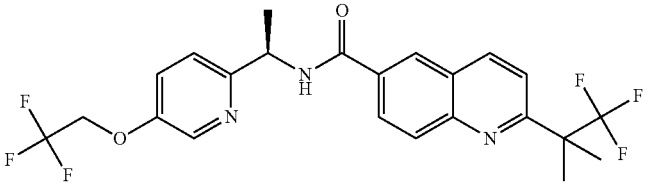
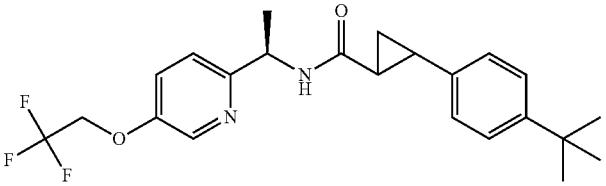
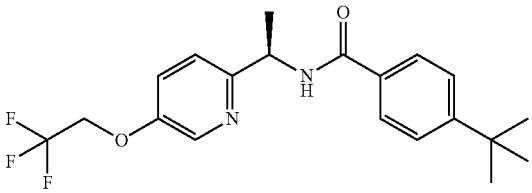
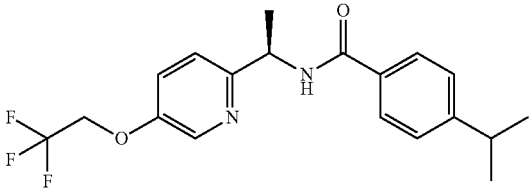
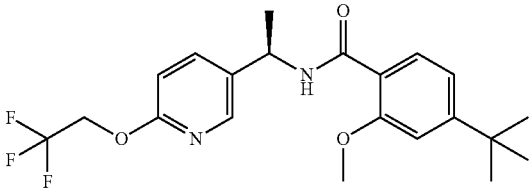
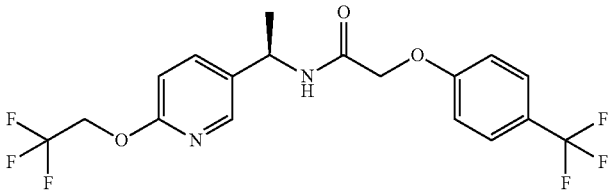
Example 9	(R)-4-(3-(1,1,1-trifluoro-2-methylpropan-2-yl)phenyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)thiazole-2-carboxamide	
Example 10	(1R,2R)-2-methyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxamide	
Example 11	(R)-2-(1,1,1-trifluoro-2-methylpropan-2-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)quinoline-6-carboxamide	
Example 12	trans-2-(4-tert-butylphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 13	(R)-4-tert-butyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 14	(R)-4-isopropyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 15	(R)-4-tert-butyl-2-methoxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)benzamide	
Example 16	(R)-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide	

TABLE 3-continued

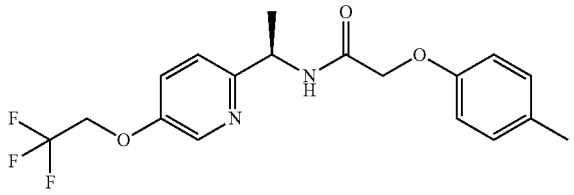
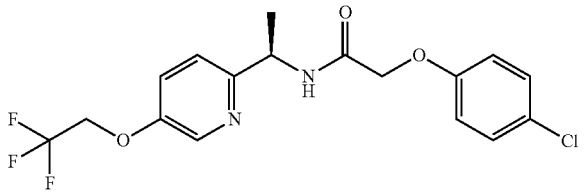
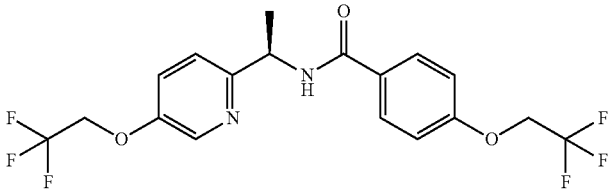
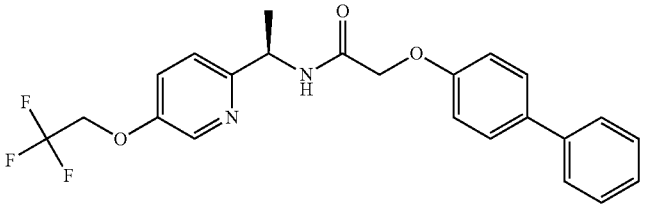
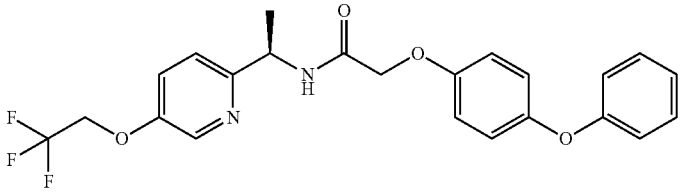
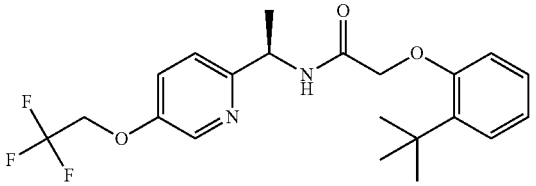
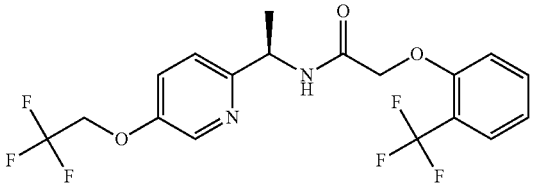
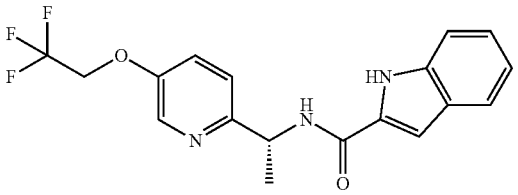
Example 17	(R)-2-(p-tolyloxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 18	(R)-2-(4-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 19	(R)-4-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 20	(R)-2-(biphenyl-4-yloxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 21	(R)-2-(4-phenoxyphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 22	(R)-2-(2-tert-butylphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 23	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(2-(trifluoromethyl)phenoxy)acetamide	
Example 24	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	

TABLE 3-continued

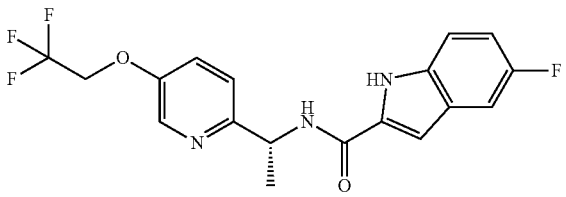
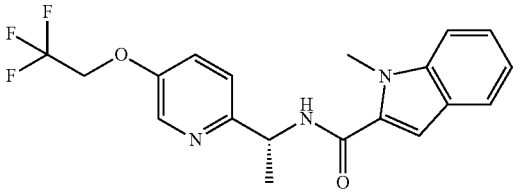
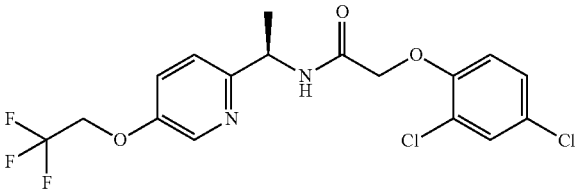
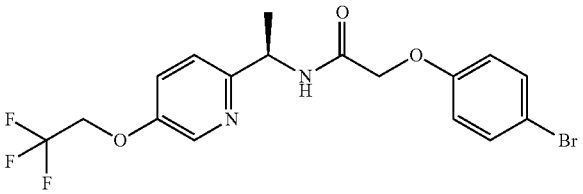
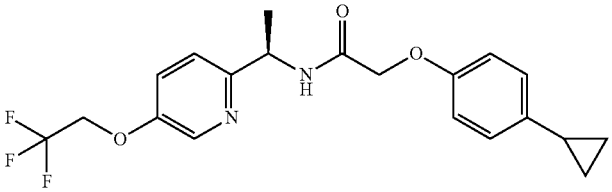
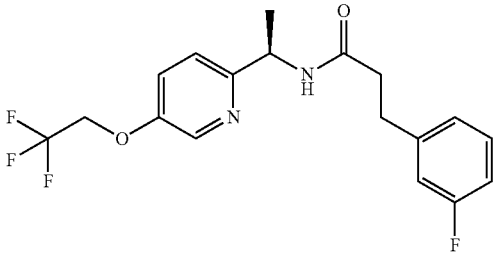
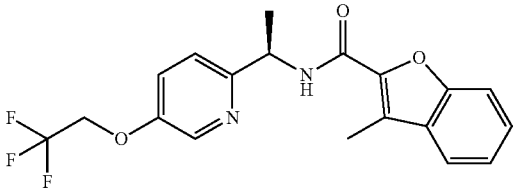
Example 25	(R)-5-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 26	(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 27	(R)-2-(2,4-dichlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 28	(R)-2-(4-bromophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 29	(R)-2-(4-cyclopropylphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 30	(R)-3-(3-fluorophenyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	
Example 31	(R)-3-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzofuran-2-carboxamide	

TABLE 3-continued

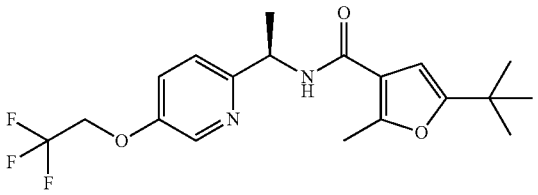
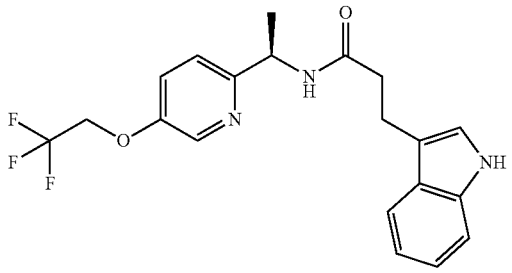
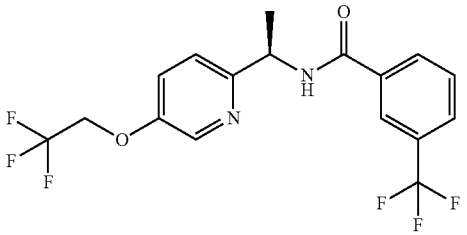
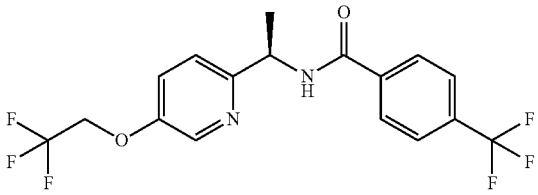
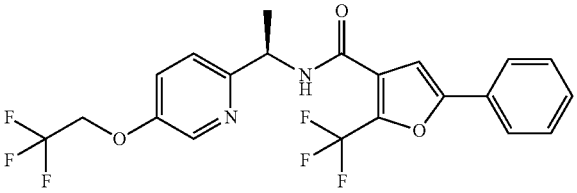
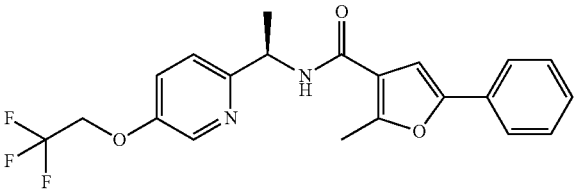
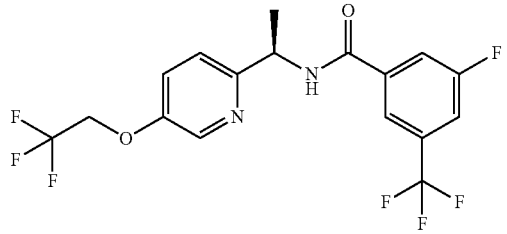
Example 32	(R)-5-butyl-butyl-2-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)furan-3-carboxamide	
Example 33	(R)-3-(1H-indol-3-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	
Example 34	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(trifluoromethyl)benzamide	
Example 35	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4-(trifluoromethyl)benzamide	
Example 36	(R)-5-phenyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(trifluoromethyl)furan-3-carboxamide	
Example 37	(R)-2-methyl-5-phenyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)furan-3-carboxamide	
Example 38	(R)-3-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethyl)benzamide	

TABLE 3-continued

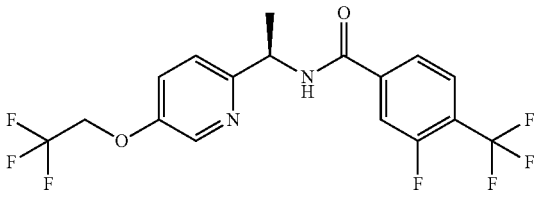
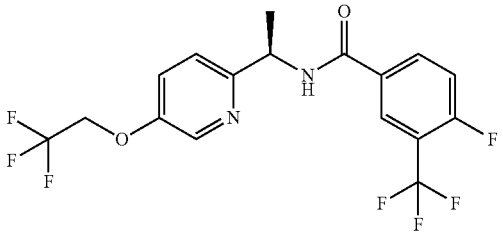
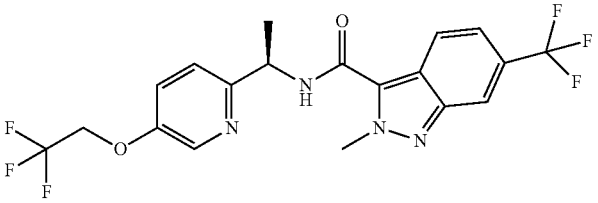
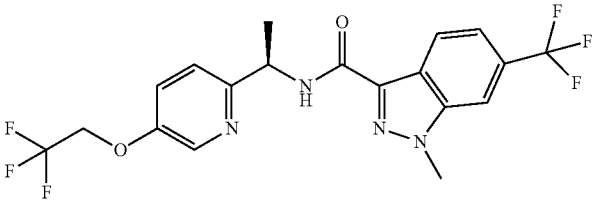
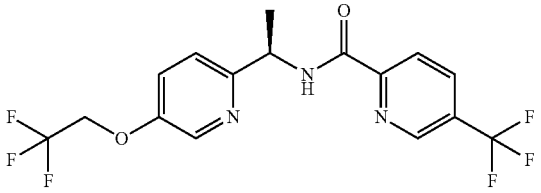
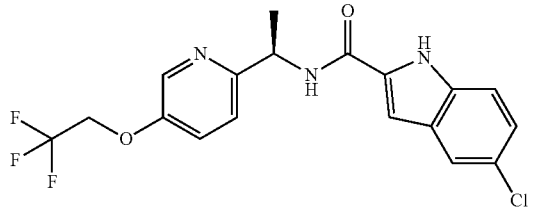
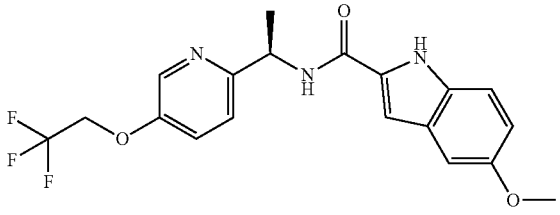
Example 39	(R)-3-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4-(trifluoromethyl)benzamide	
Example 40	(R)-4-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(trifluoromethyl)benzamide	
Example 41	(R)-2-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-6-(trifluoromethyl)-2H-indazole-3-carboxamide	
Example 42	(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-6-(trifluoromethyl)-1H-indazole-3-carboxamide	
Example 43	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethyl)picolinamide	
Example 44	(R)-5-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 45	(R)-5-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	

TABLE 3-continued

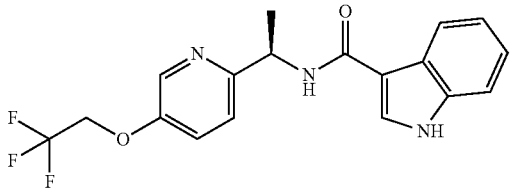
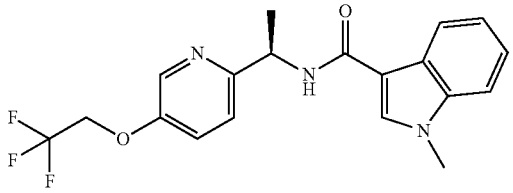
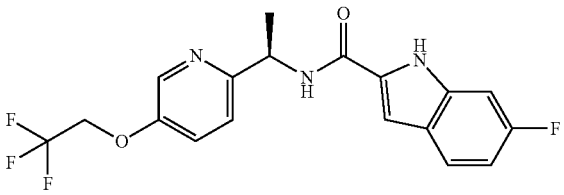
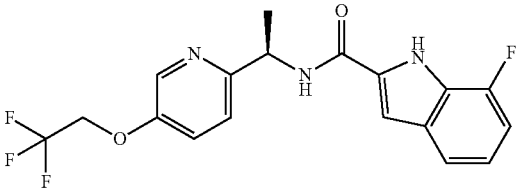
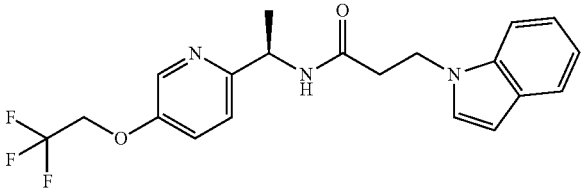
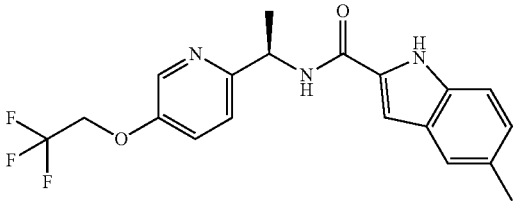
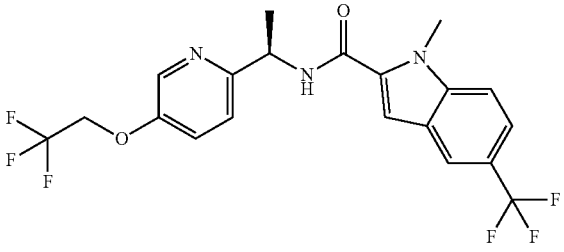
Example 46	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 47	(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 48	(R)-5-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 49	(R)-7-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 50	(R)-3-(1H-Indol-1-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	
Example 51	(R)-5-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl-1H-indole-2-carboxamide	
Example 52	(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethyl)-1H-indole-2-carboxamide	

TABLE 3-continued

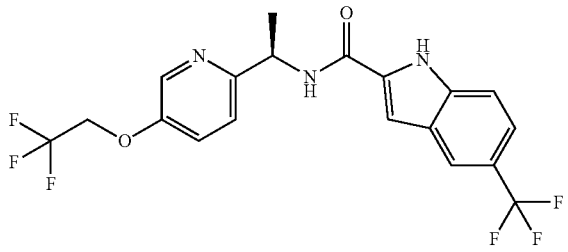
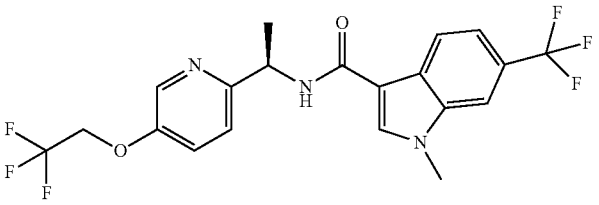
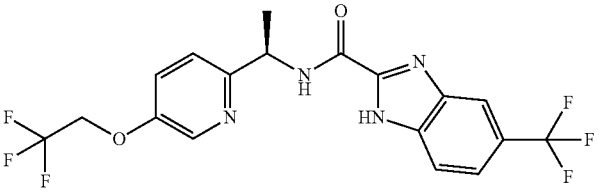
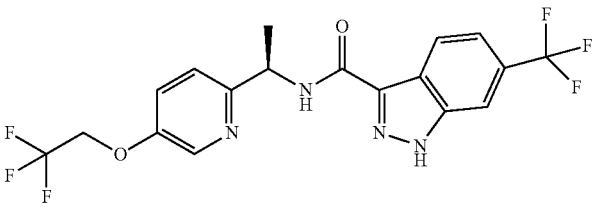
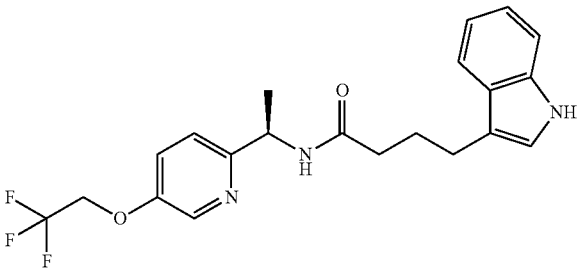
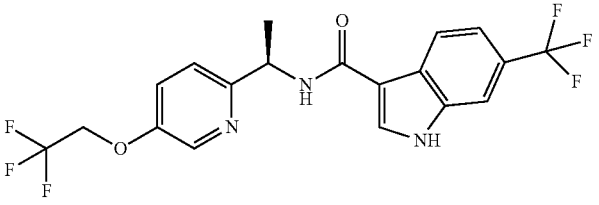
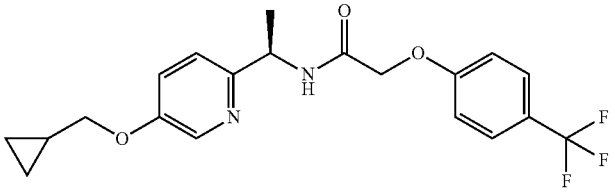
Example 53	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethyl)-1H-indole-2-carboxamide	
Example 54	(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-6-(trifluoromethyl)-1H-indole-3-carboxamide	
Example 55	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethyl)-1H-benzo[d]imidazole-2-carboxamide	
Example 56	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-6-(trifluoromethyl)-1H-indazole-3-carboxamide	
Example 57	(R)-4-(1H-indol-3-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)butanamide	
Example 58	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-6-(trifluoromethyl)-1H-indole-3-carboxamide	
Example 59	(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoro-methyl)phenoxy)acetamide	

TABLE 3-continued

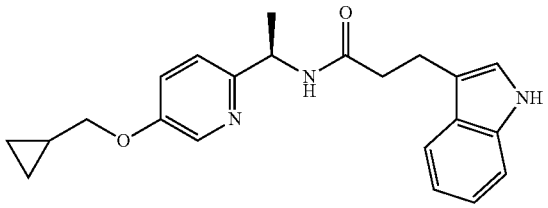
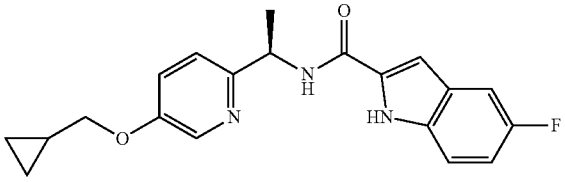
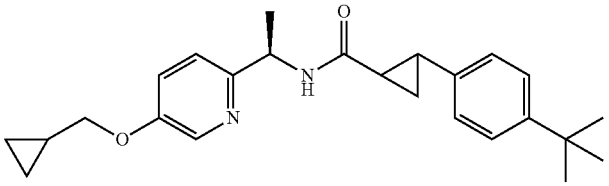
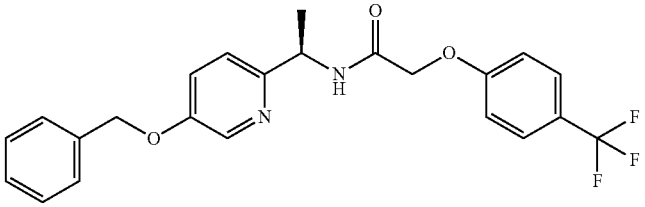
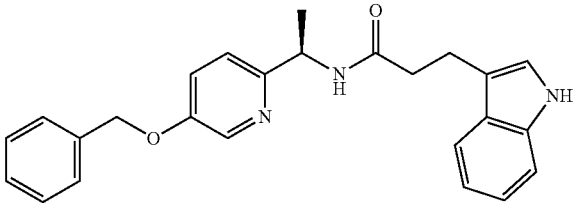
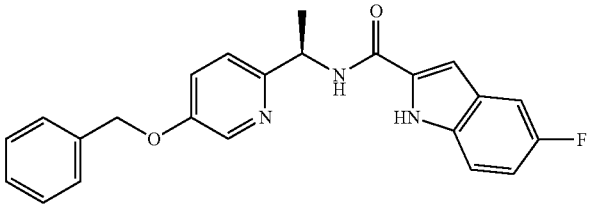
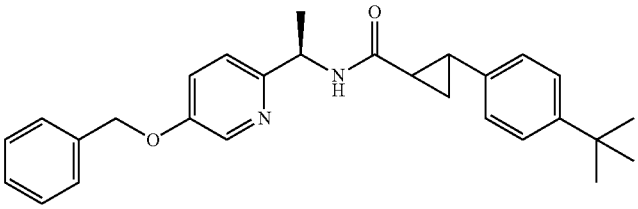
Example 60	(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-3-(1H-indol-3-yl)propanamide	
Example 61	(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-5-fluoro-1H-indole-2-carboxamide	
Example 62	trans-2-(4-tert-butylphenyl)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)cyclopropane-carboxamide	
Example 63	(R)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide	
Example 64	(R)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-3-(1H-indol-3-yl)propanamide	
Example 65	(R)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-5-fluoro-1H-indole-2-carboxamide	
Example 66	trans-N-((R)-1-(5-(benzyloxy)pyridin-2-yl)ethyl)-2-(4-tert-butylphenyl) cyclopropanecarboxamide	

TABLE 3-continued

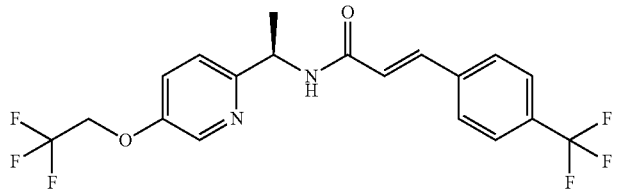
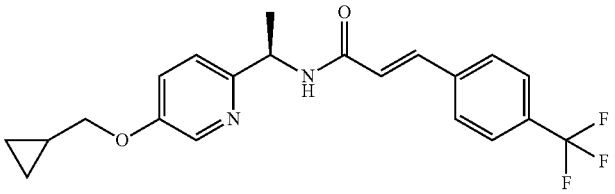
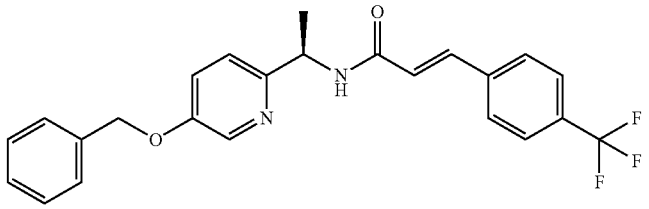
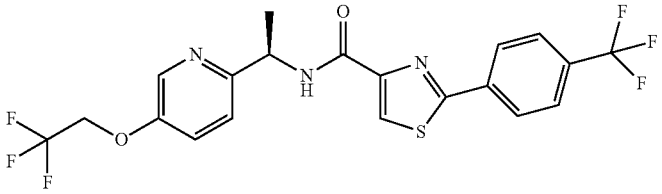
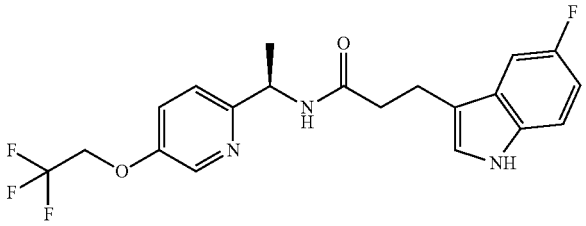
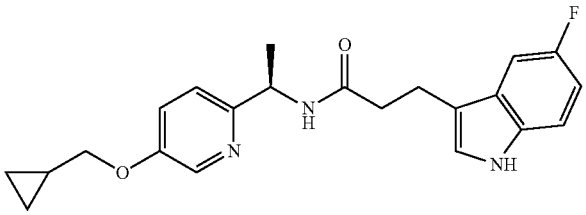
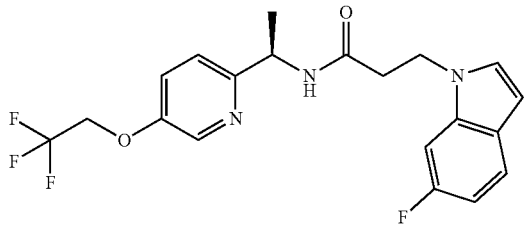
Example 67	(R,E)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(4-(trifluoromethyl)phenyl)acrylamide	
Example 68	(R,E)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-3-(4-(trifluoromethyl)phenyl)acrylamide	
Example 69	(R,E)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-3-(4-(trifluoromethyl)phenyl)acrylamide	
Example 70	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)thiazole-4-carboxamide	
Example 71	(R)-3-(5-fluoro-1H-indol-3-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	
Example 72	(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-3-(5-fluoro-1H-indol-3-yl)propanamide	
Example 73	(R)-3-(6-fluoro-1H-indol-1-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	

TABLE 3-continued

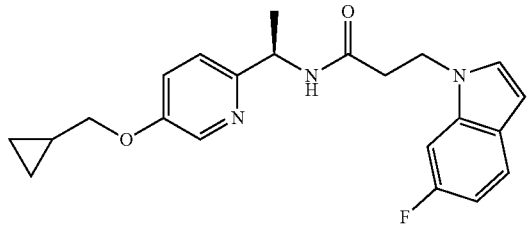
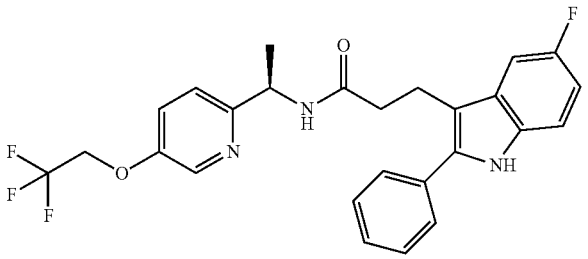
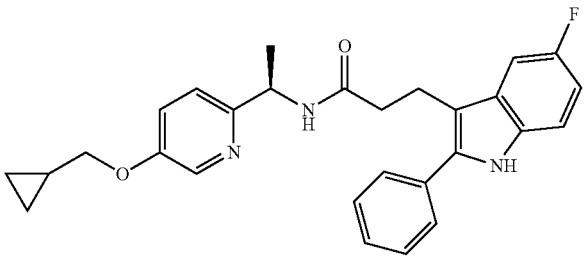
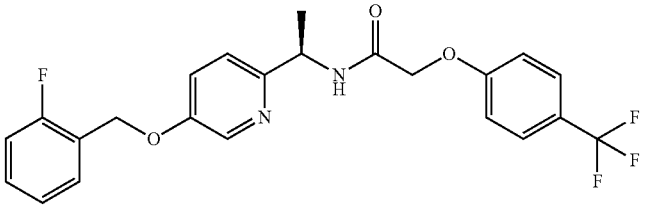
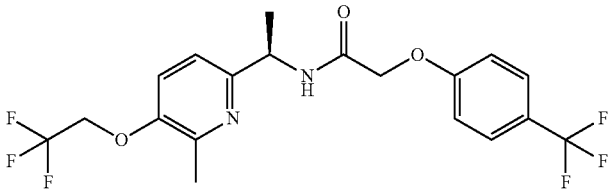
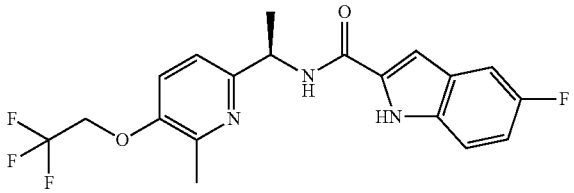
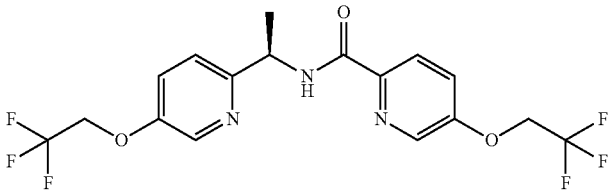
Example 74	(R)-N-(1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-3-(6-fluoro-1H-indol-1-yl)propanamide	
Example 75	(R)-3-(5-fluoro-2-phenyl-1H-indol-3-yl)-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)propanamide	
Example 76	(R)-N-(1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-3-(5-fluoro-2-phenyl-1H-indol-3-yl)propanamide	
Example 77	(R)-N-(1-(5-(2-fluorobenzyloxy) pyridin-2-yl)ethyl)-2-(4-(trifluoro-methyl)phenoxy)acetamide	
Example 78	(R)-N-(1-(6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoro-methyl)phenoxy)acetamide	
Example 79	(R)-5-fluoro-N-(1-(6-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 80	(R)-5-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)picolinamide	

TABLE 3-continued

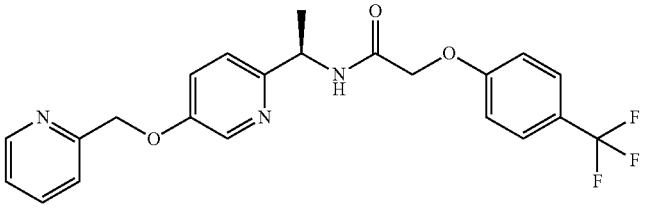
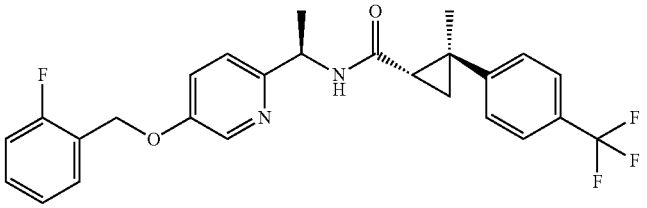
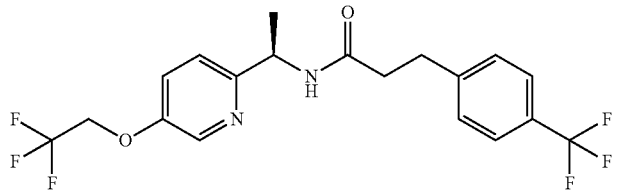
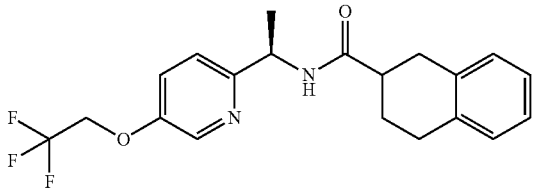
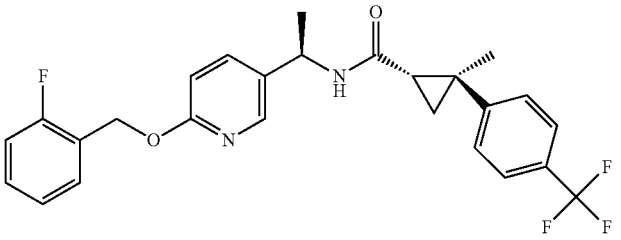
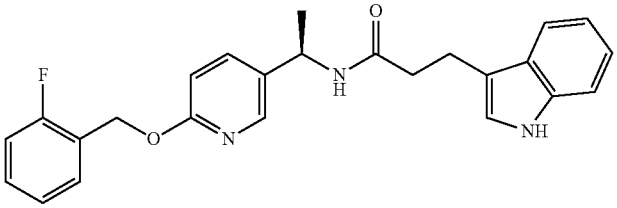
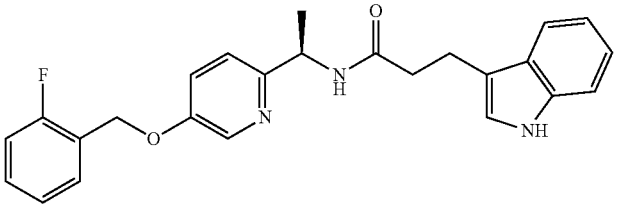
Example 81	(R)-N-(1-(5-(pyridin-2-ylmethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy) acetamide	
Example 82	(1S,2S)-N-((R)-1-(5-(2-fluorobenzyloxy)pyridin-2-yl)ethyl)-2-methyl-2-(4-(trifluoromethyl)phenyl) cyclopropanecarboxamide	
Example 83	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(4-(trifluoromethyl)phenyl)propanamide	
Example 84	N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxamide	
Example 85	(1S,2S)-N-((R)-1-(6-(2-fluorobenzyloxy)pyridin-3-yl)ethyl)-2-methyl-2-(4-(trifluoromethyl)phenyl) cyclopropanecarboxamide	
Example 86	(R)-N-(1-(6-(2-fluorobenzyloxy)pyridin-3-yl)ethyl)-3-(1H-indol-3-yl)propanamide	
Example 87	(R)-N-(1-(5-(2-fluorobenzyloxy)pyridin-2-yl)ethyl)-3-(1H-indol-3-yl)propanamide	

TABLE 3-continued

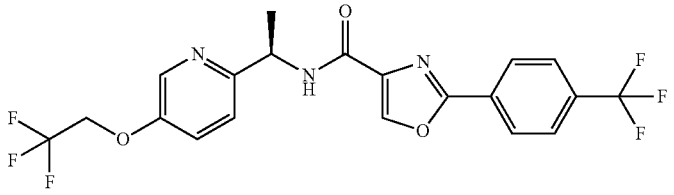
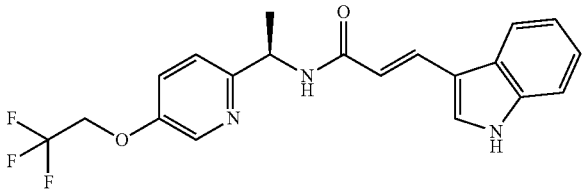
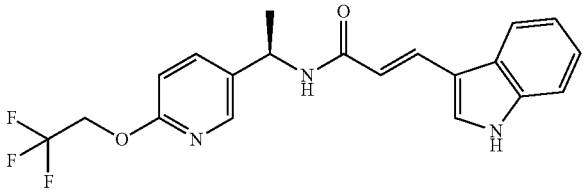
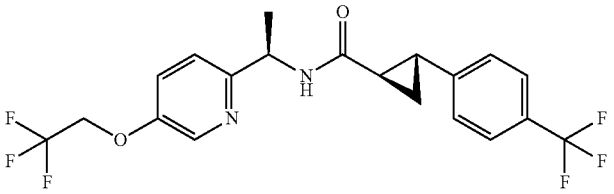
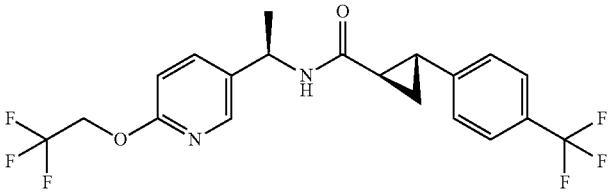
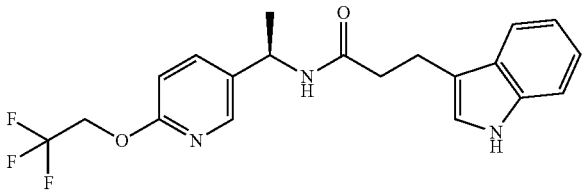
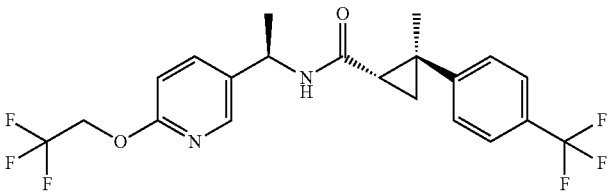
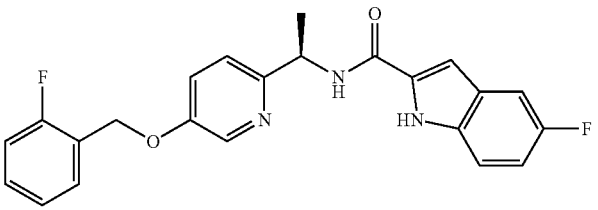
Example 88	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)oxazole-4-carboxamide	
Example 89	(R,E)-3-(1H-indol-3-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acrylamide	
Example 90	(R,E)-3-(1H-indol-3-yl)-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)acrylamide	
Example 91	(1R,2R)-N-((R)-1-(5-(2,2,2-trifluoro-ethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoro-methyl)phenyl) cyclopropanecarboxamide	
Example 92	(1R,2R)-N-((R)-1-(6-(2,2,2-trifluoro-ethoxy)pyridin-3-yl)ethyl)-2-(4-(trifluoro-methyl)phenyl) cyclopropanecarboxamide	
Example 93	(R)-3-(1H-Indol-3-yl)-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)propanamide	
Example 94	(1S,2S)-2-methyl-N-((R)-1-(6-(2,2,2-trifluoro-ethoxy)pyridin-3-yl)ethyl)-2-(4-(trifluoro-methyl)phenyl) cyclopropanecarboxamide	
Example 95	(R)-5-fluoro-N-(1-(5-(2-fluorobenzyloxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	

TABLE 3-continued

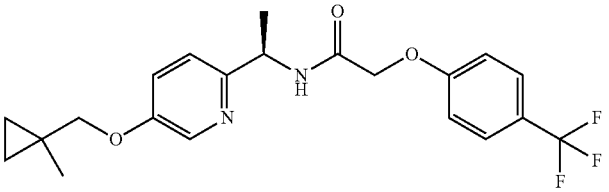
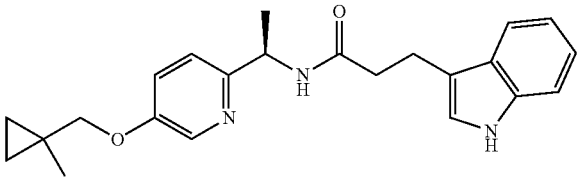
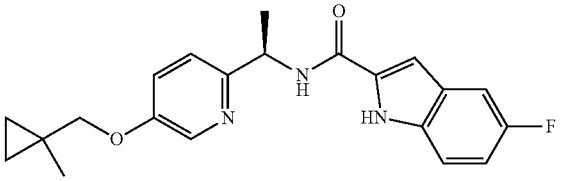
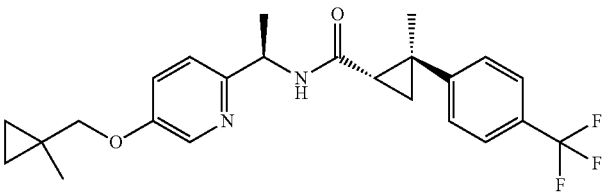
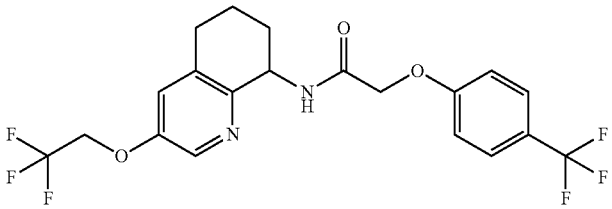
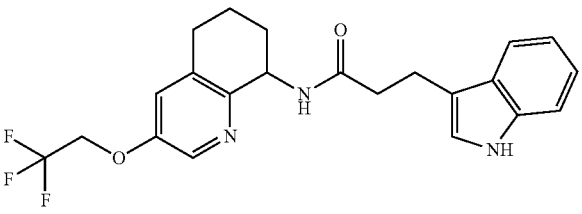
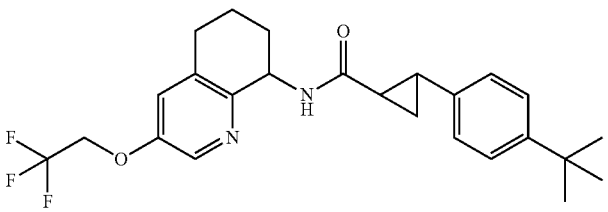
Example 96	(R)-N-(1-(5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide	
Example 97	(R)-3-(1H-indol-3-yl)-N-(1-(5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)ethyl)propanamide	
Example 98	(R)-5-fluoro-N-(1-(5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 99	(1S,2S)-2-methyl-N-((R)-1-(5-((1-methylcyclopropyl)methoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxamide	
Example 100	N-(3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinolin-8-yl)-2-(4-(trifluoromethyl)phenoxy)acetamide	
Example 101	3-(1H-indol-3-yl)-N-(3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinolin-8-yl)propanamide	
Example 102	trans-2-(4-tert-butylphenyl)-N-(3-(2,2,2-trifluoroethoxy)-5,6,7,8-tetrahydroquinolin-8-yl)cyclopropanecarboxamide	

TABLE 3-continued

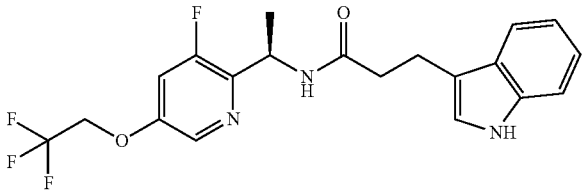
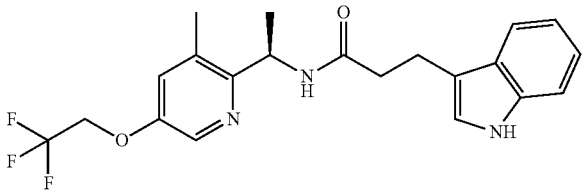
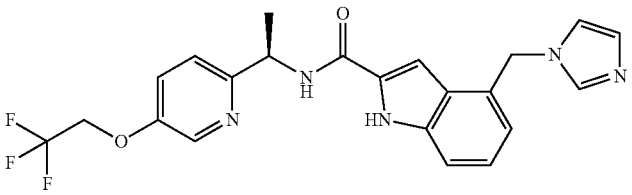
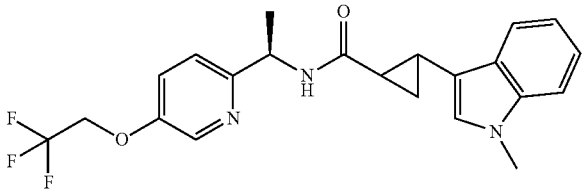
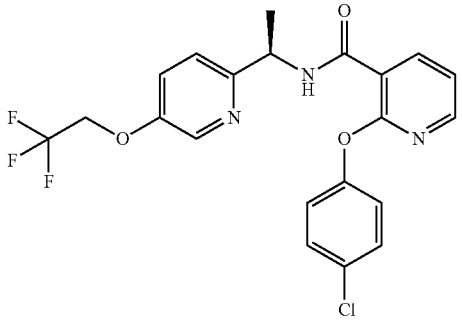
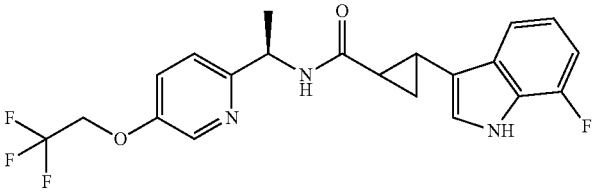
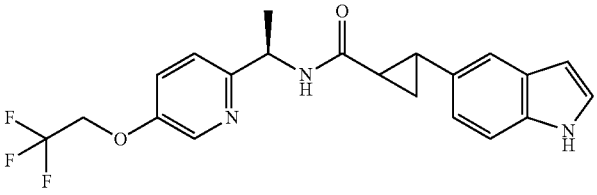
Example 103	(R)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(1H-indol-3-yl)propanamide	
Example 104	(R)-3-(1H-indol-3-yl)-N-(1-(3-methyl-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	
Example 105	(R)-4-((1H-imidazol-1-yl)methyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 106	trans-2-(1-methyl-1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 107	(R)-2-(4-chlorophenexyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)nicotinamide	
Example 108	trans-2-(7-fluoro-1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 109	trans-2-(1H-indol-5-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl) cyclopropanecarboxamide	

TABLE 3-continued

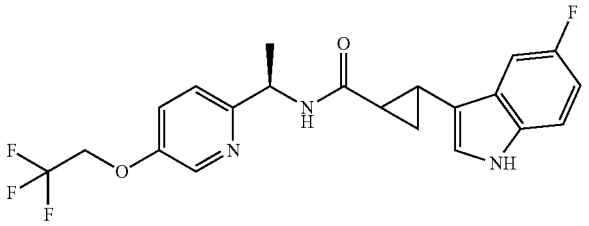
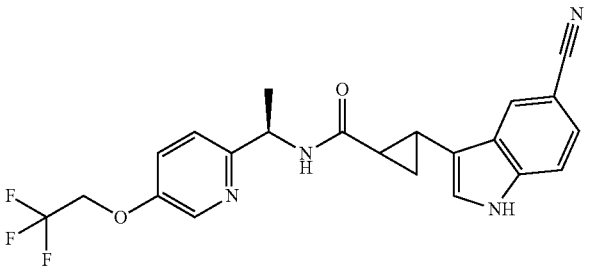
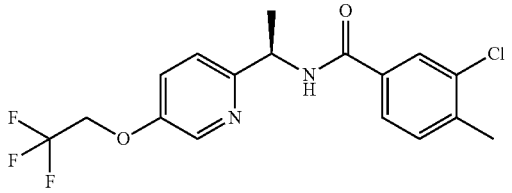
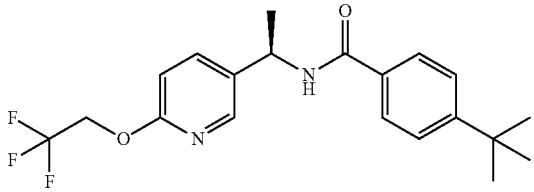
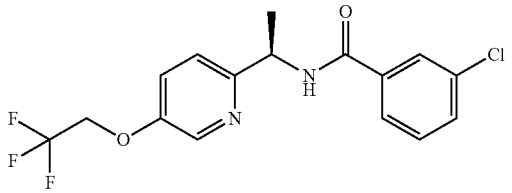
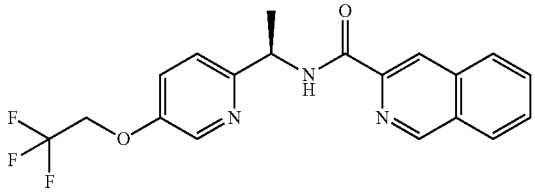
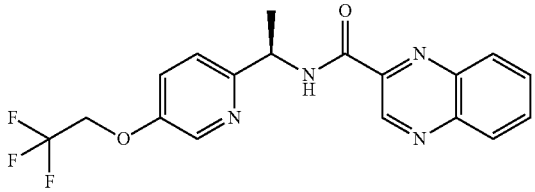
Example 110	trans-2-(5-fluoro-1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 111	trans-2-(5-cyano-1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 112	(R)-3-chloro-4-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 113	(R)-4-tert-butyl-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)benzamide	
Example 114	(R)-3-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 115	(R)-3-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)isoquinoline-3-carboxamide	
Example 116	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)quinoxaline-2-carboxamide	

TABLE 3-continued

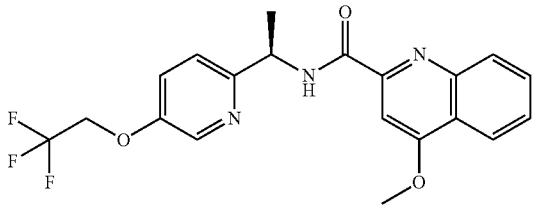
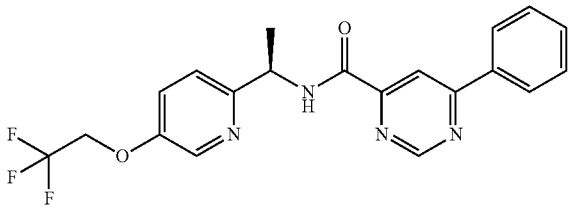
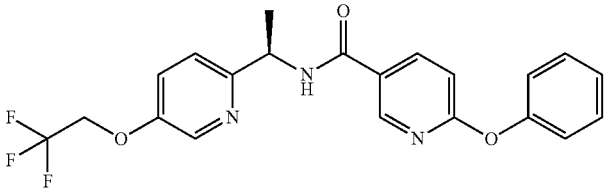
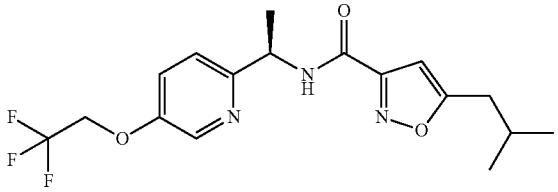
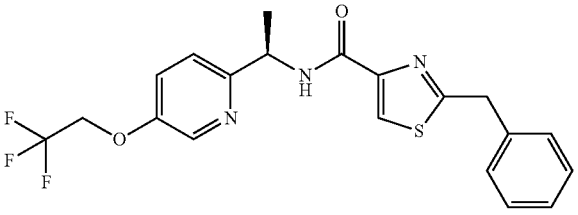
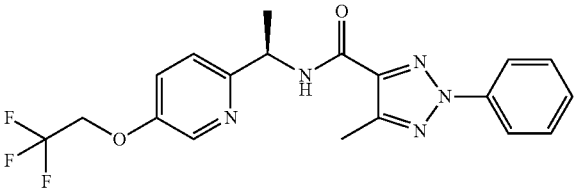
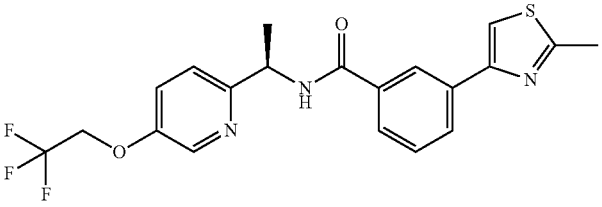
Example 117	(R)-4-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)quinoline-2-carboxamide	
Example 118	(R)-6-phenyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)pyrimidine-4-carboxamide	
Example 119	(R)-6-phenoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)nicotinamide	
Example 120	(R)-5-isobutyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)isoxazole-3-carboxamide	
Example 121	(R)-2-benzyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)thiazole-4-carboxamide	
Example 122	(R)-5-methyl-2-phenyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2H-1,2,3-triazole-4-carboxamide	
Example 123	(R)-3-(2-methylthiazol-4-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	

TABLE 3-continued

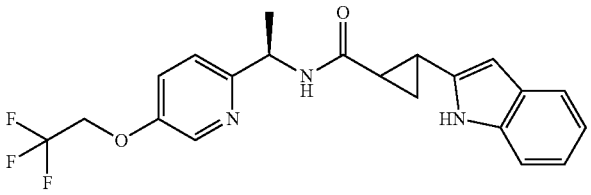
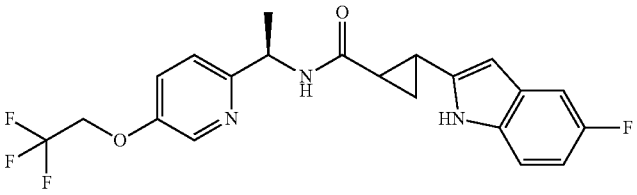
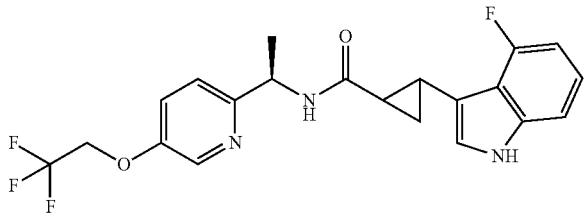
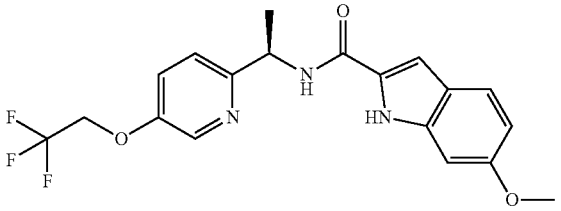
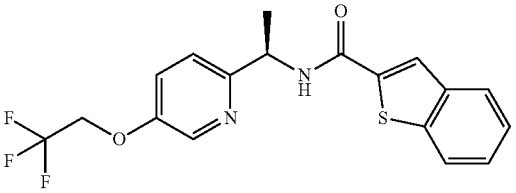
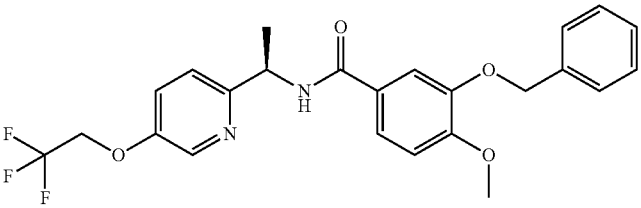
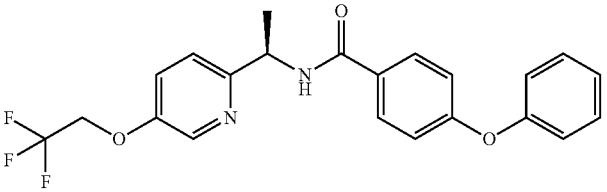
Example 124	trans-2-(1H-indol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 125	trans-2-(5-fluoro-1H-indol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 126	trans-2-(4-fluoro-1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 127	(R)-6-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 128	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzo[b]thiophene-2-carboxamide	
Example 129	(R)-3-(benzyloxy)-4-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 130	(R)-4-phenoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	

TABLE 3-continued

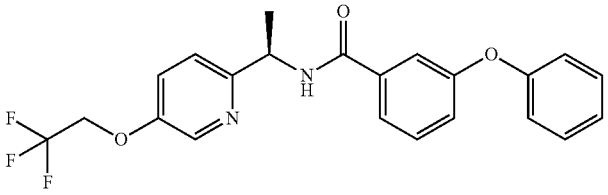
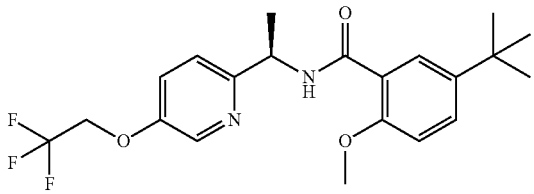
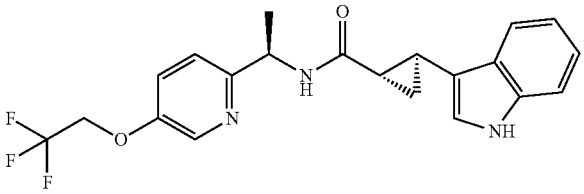
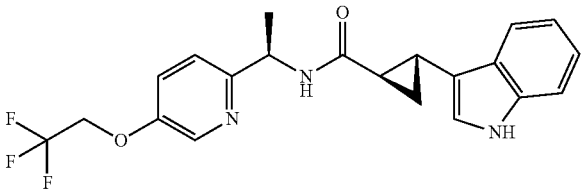
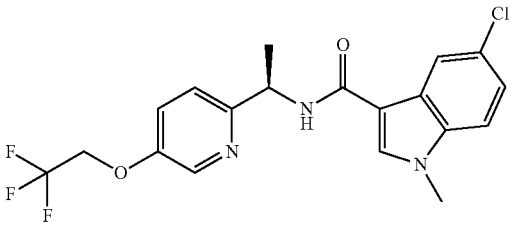
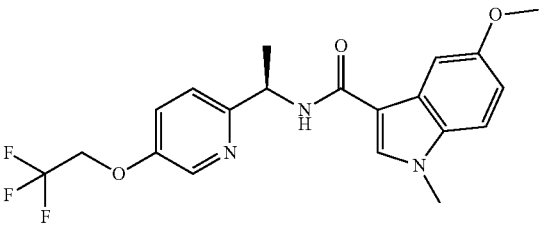
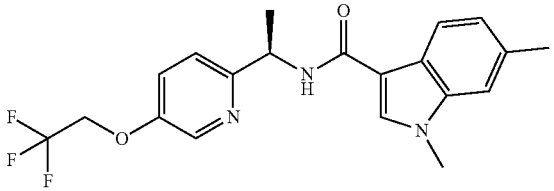
Example 131	(R)-3-phenoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 132	(R)-5-tert-butyl-2-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 133	(1S*,2S*)-2-(1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 134	(1R*,2R*)-2-(1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 135	(R)-5-chloro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 136	(R)-5-methoxy-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 137	(R)-1,6-dimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	

TABLE 3-continued

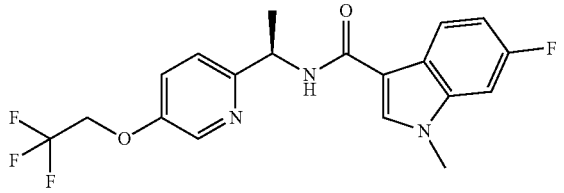
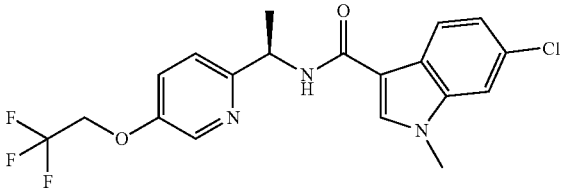
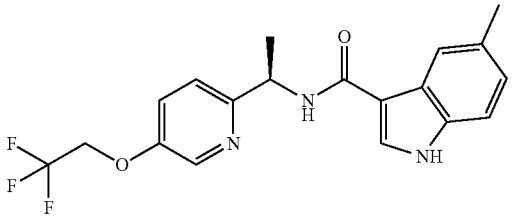
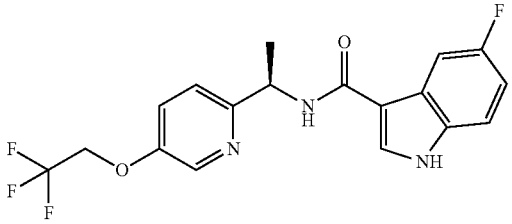
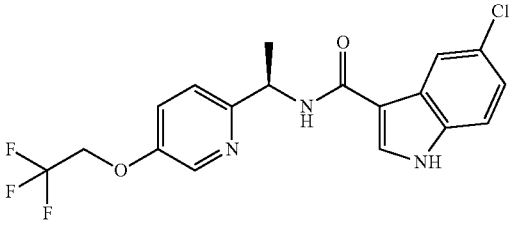
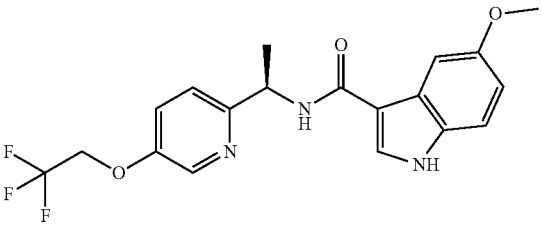
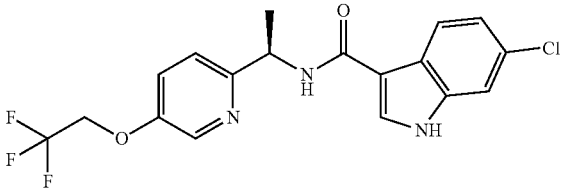
Example 138	(R)-6-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 139	(R)-6-chloro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 140	(R)-5-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 141	(R)-5-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 142	(R)-5-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 143	(R)-5-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	
Example 144	(R)-6-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-3-carboxamide	

TABLE 3-continued

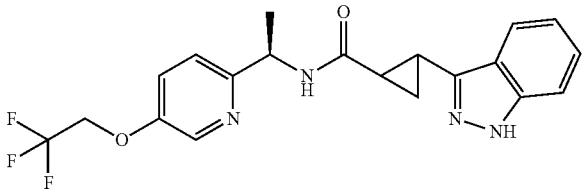
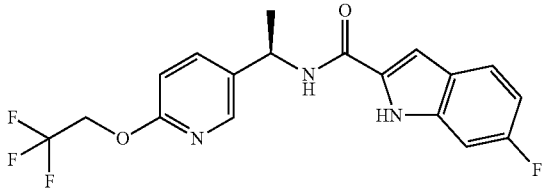
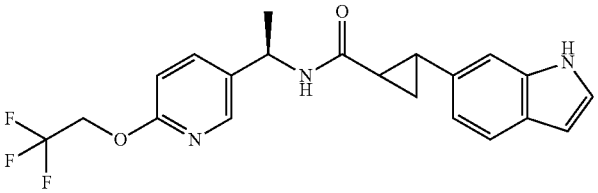
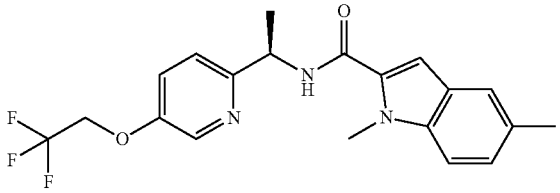
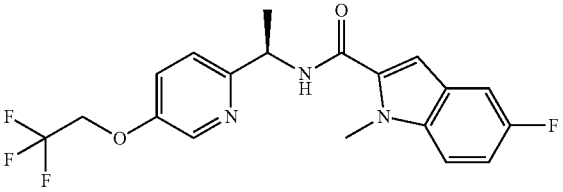
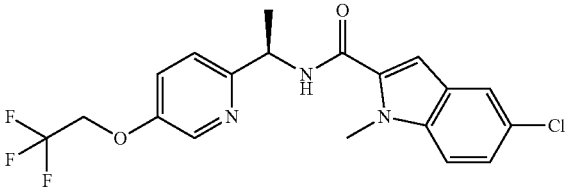
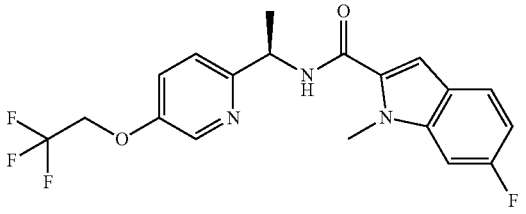
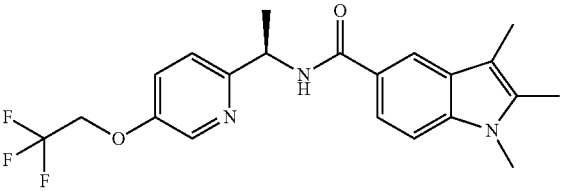
Example 145	trans-2-(1H-indazol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 146	(R)-6-fluoro-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-1H-indole-2-carboxamide	
Example 147	trans-2-(1H-indol-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 148	(R)-1,5-dimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 149	(R)-5-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 150	(R)-5-chloro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 151	(R)-6-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 152	(R)-1,2,3-trimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-5-carboxamide	

TABLE 3-continued

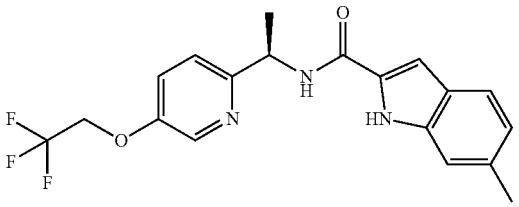
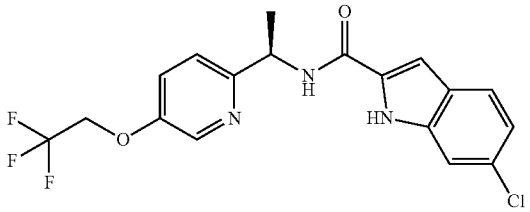
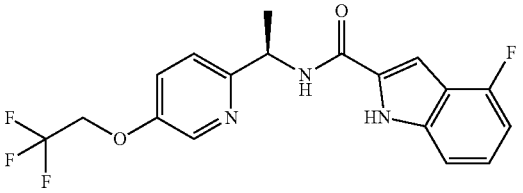
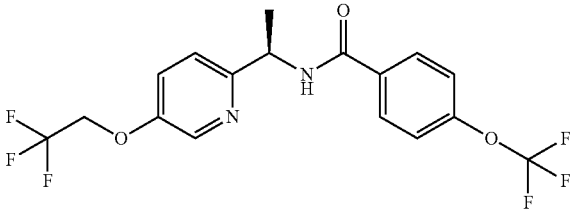
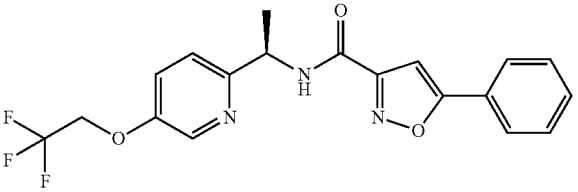
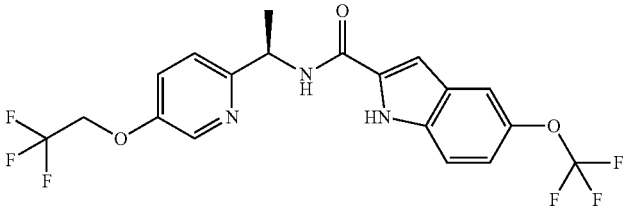
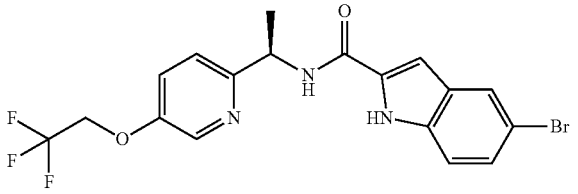
Example 153	(R)-6-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 154	(R)-6-chloro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 155	(R)-4-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 156	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4-(trifluoromethoxy)benzamide	
Example 157	(R)-5-phenyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)isoxazole-3-carboxamide	
Example 158	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethoxy)-1H-indole-2-carboxamide	
Example 159	(R)-5-bromo-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	

TABLE 3-continued

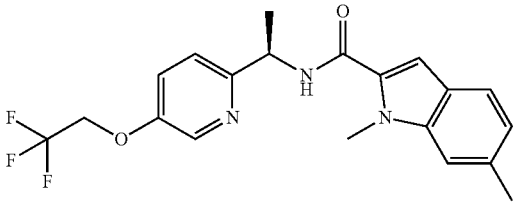
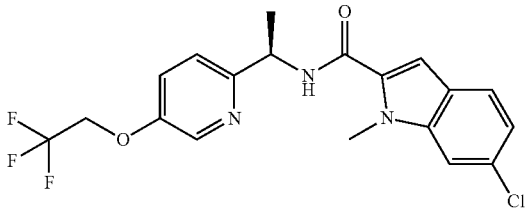
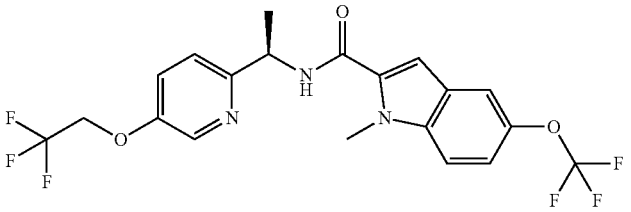
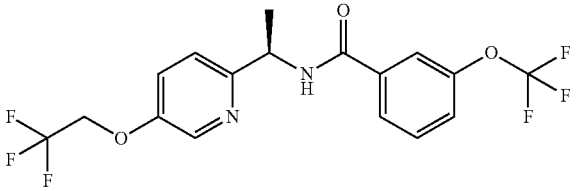
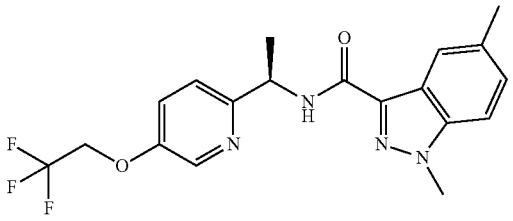
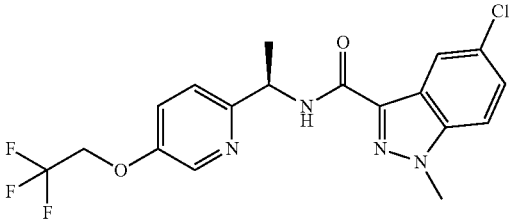
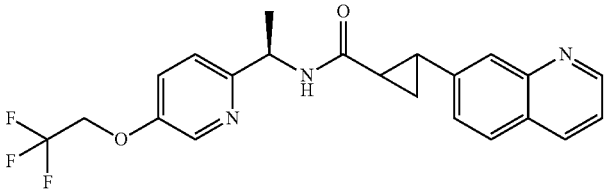
Example 160	(R)-1,6-dimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 161	(R)-6-chloro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 162	(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-5-(trifluoromethoxy)-1H-indole-2-carboxamide	
Example 163	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(trifluoromethoxy)benzamide	
Example 164	(R)-1,5-dimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indazole-3-carboxamide	
Example 165	(R)-5-chloro-1-methyl-N-(1-(5-(2,2,2-trifluomethoxy)pyridin-2-yl)ethyl)-1H-indazole-3-carboxamide	
Example 166	trans-2-(quinolin-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarbaxamide	

TABLE 3-continued

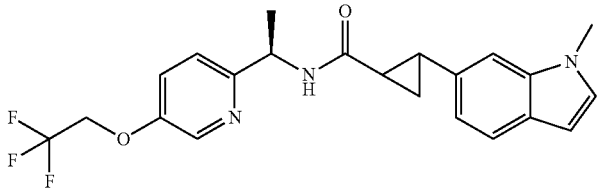
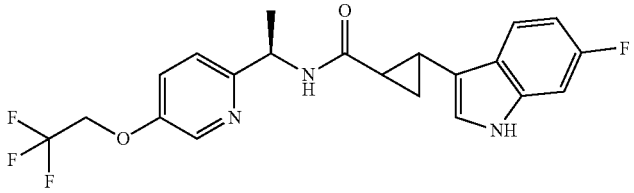
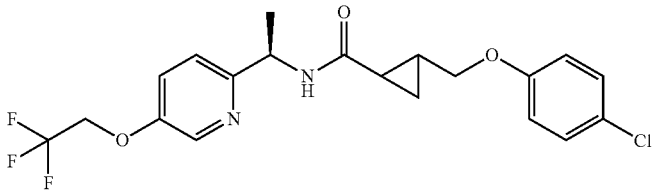
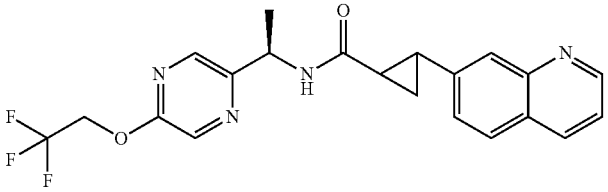
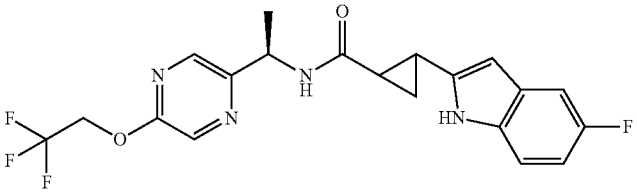
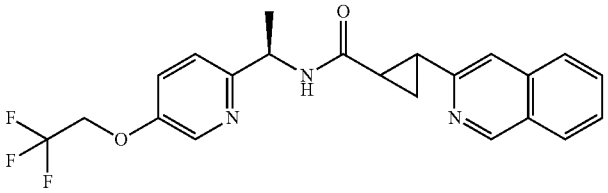
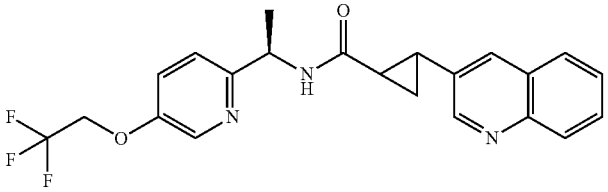
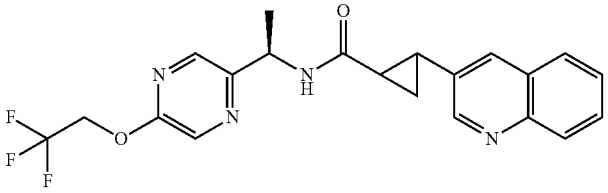
Example 167	trans-2-(1-methyl-1H-indol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 168	trans-2-(6-fluoro-1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 169	trans-2-((4-chlorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 170	trans-2-(quinolin-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 171	trans-2-(5-fluoro-1H-indol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 172	trans-2-(isoquinolin-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 173	trans-2-(quinolin-3-yl)-N-(R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 174	trans-2-(quinolin-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

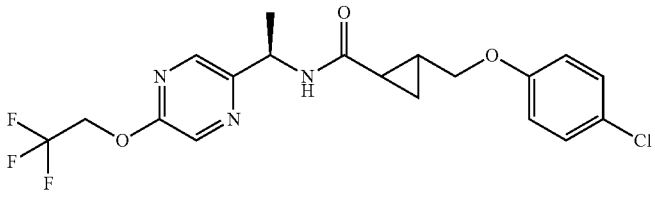
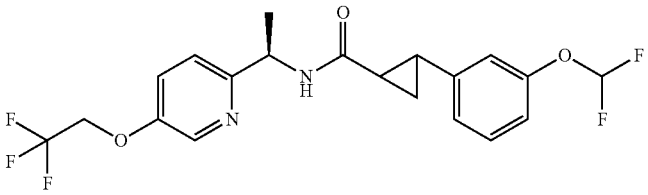
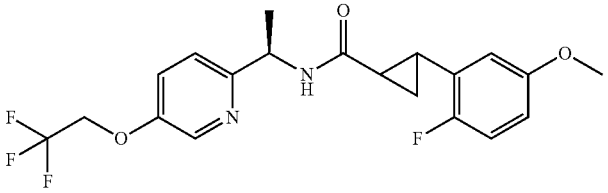
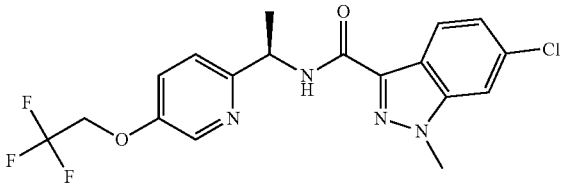
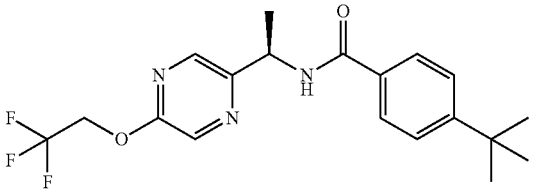
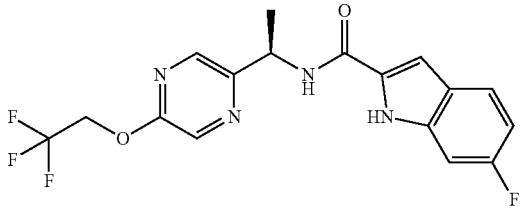
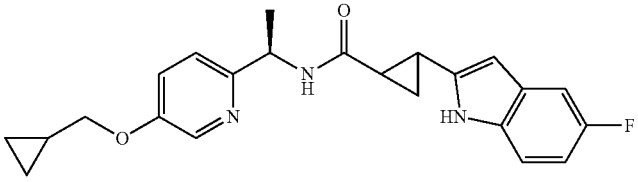
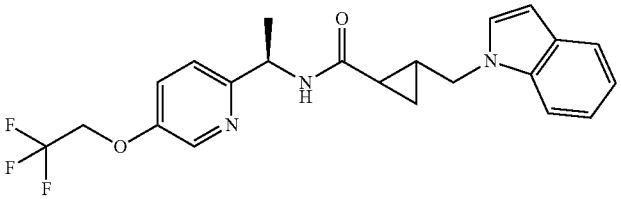
Example 175	trans-2-((4-chlorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 176	trans-2-(3-(difluoromethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 177	trans-2-(2-fluoro-5-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 178	(R)-6-chloro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indazole-3-carboxamide	
Example 179	(R)-4-tert-butyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)benzamide	
Example 180	(R)-6-fluoro-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 181	trans-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-2-yl)cyclopropanecarboxamide	
Example 182	trans-2-((1H-indol-1-yl)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

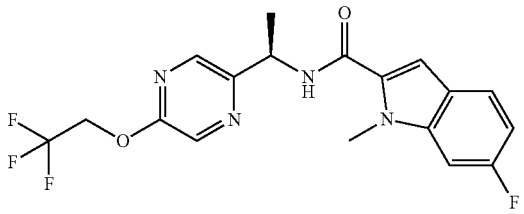
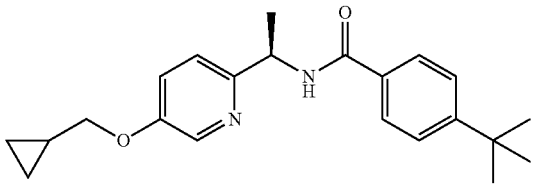
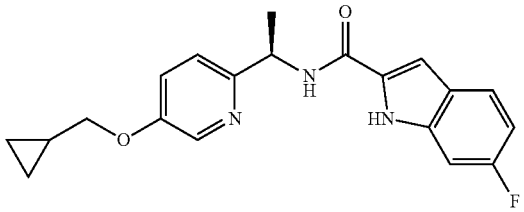
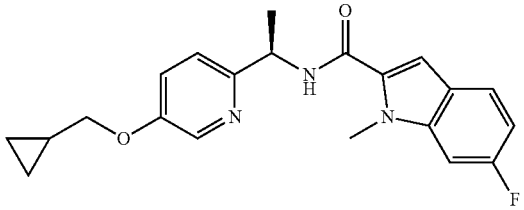
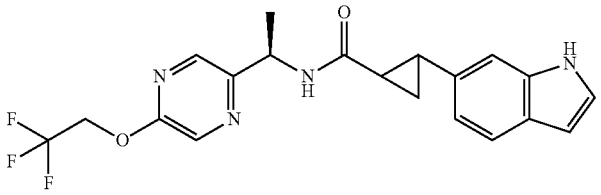
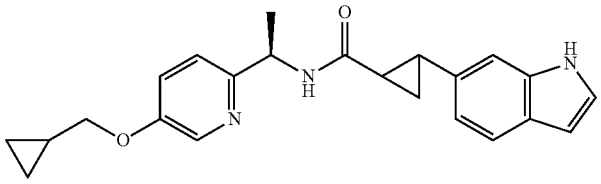
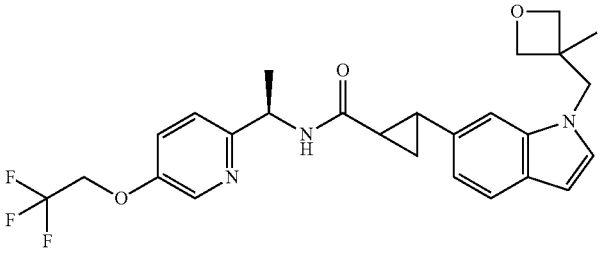
Example 183	(R)-6-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 184	(R)-4-tert-butyl-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)benzamide	
Example 185	(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-6-fluoro-1H-indole-2-carboxamide	
Example 186	(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-6-fluoro-1-methyl-1H-indole-2-carboxamide	
Example 187	trans-2-(1H-indol-6-yl)-N-(R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 188	trans-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(1H-indol-6-yl)cyclopropanecarboxamide	
Example 189	trans-2-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoro-ethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

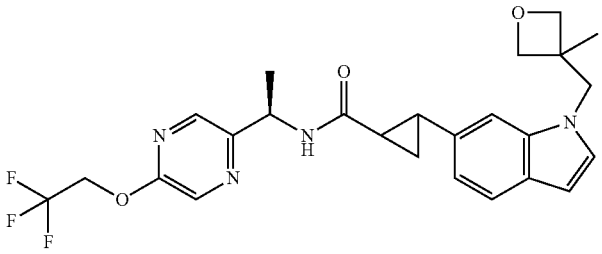
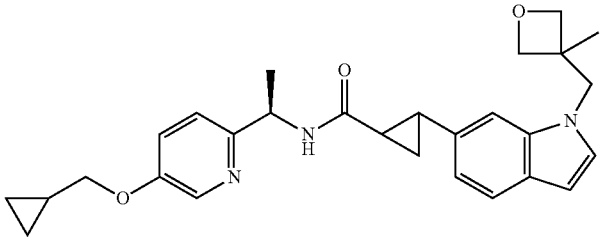
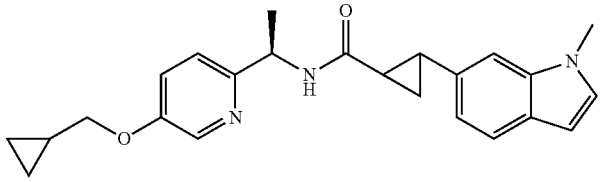
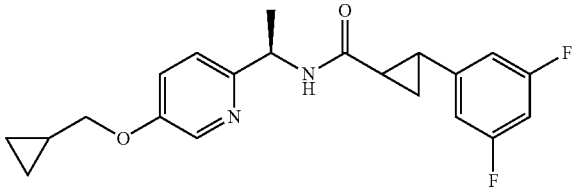
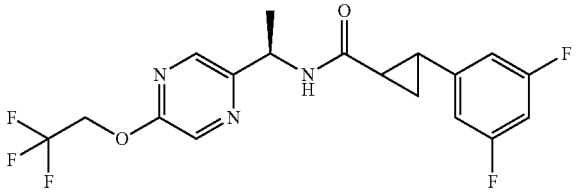
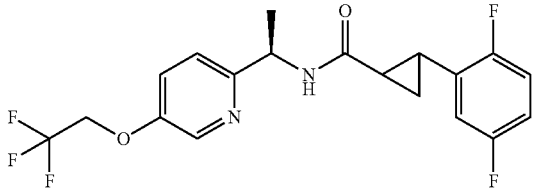
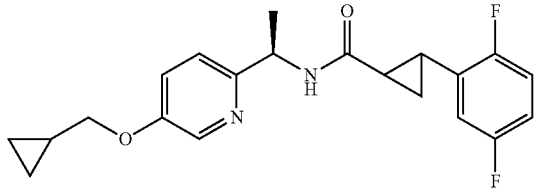
Example 190	trans-2-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoro-ethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 191	trans-N-((R)-1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-2-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)cyclopropanecarboxamide	
Example 192	trans-N-((R)-1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-2-(1-methyl-1H-indol-6-yl)cyclopropanecarboxamide	
Example 193	trans-N-((R)-1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-2-(3,5-difluorophenyl) cyclopropanecarboxamide	
Example 194	trans-2-(3,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 195	trans-2-(2,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 196	trans-N-((R)-1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-2-(2,5-difluorophenyl) cyclopropanecarboxamide	

TABLE 3-continued

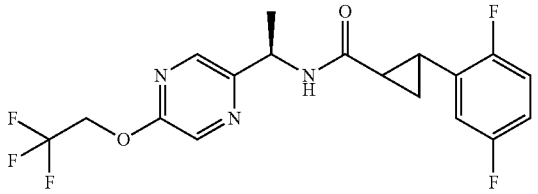
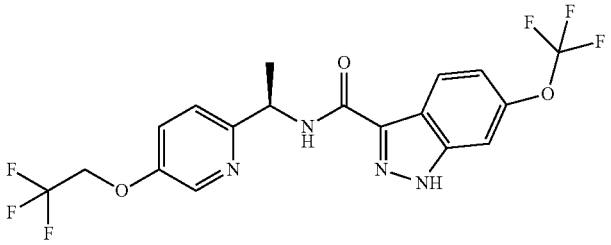
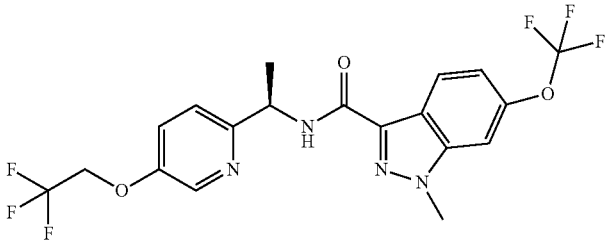
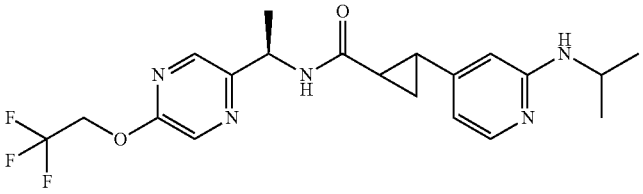
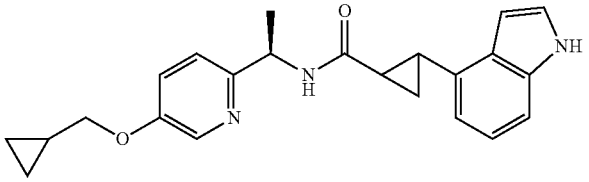
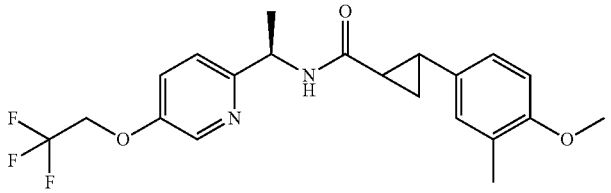
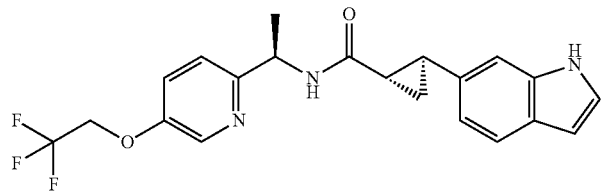
Example 197	trans-2-(2,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 198	(R)-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)-6-(trifluoromethoxy)-1H-indazole-3-carboxamide	
Example 199	(R)-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)-6-(trifluoromethoxy)-1H-indazole-3-carboxamide	
Example 200	trans-2-(2-(isopropylamino)pyridin-4-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 201	trans-N-((R)-1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-2-(1H-indol-4-yl)cyclopropanecarboxamide	
Example 202	trans-2-(4-methoxy-3-methylphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 203	(1S*,2S*)-2-(1H-indol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

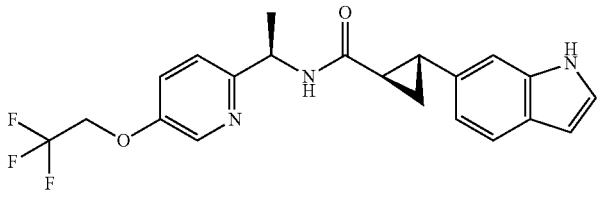
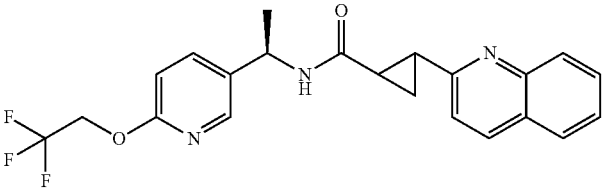
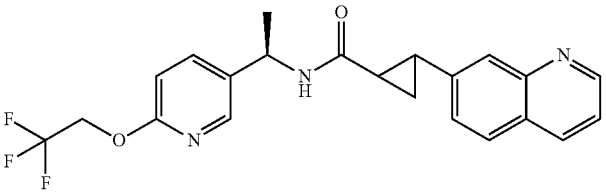
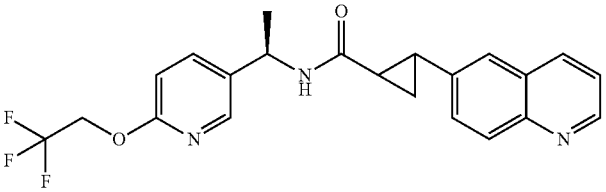
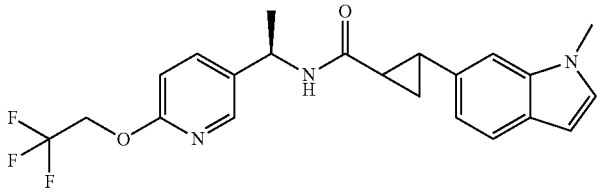
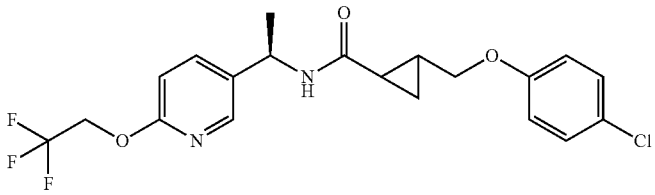
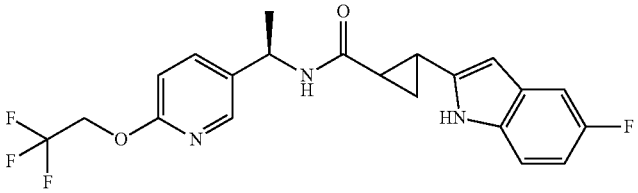
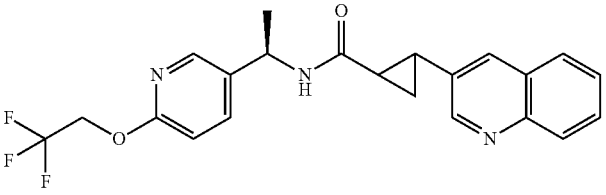
Example 204	(1R*,2R*)-2-(1H-indol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 205	trans-2-(quinolin-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 206	trans-2-(quinolin-7-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 207	trans-2-(quinolin-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 208	trans-2-(1-methyl-1H-indol-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 209	trans-2-((4-chlorophenoxy)methyl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 210	trans-2-(5-fluoro-1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 211	trans-2-(quinolin-3-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

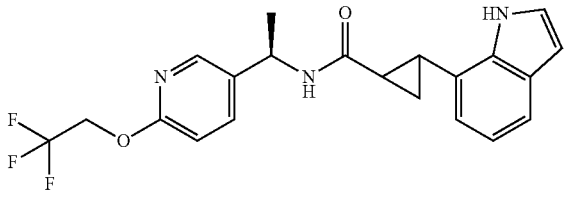
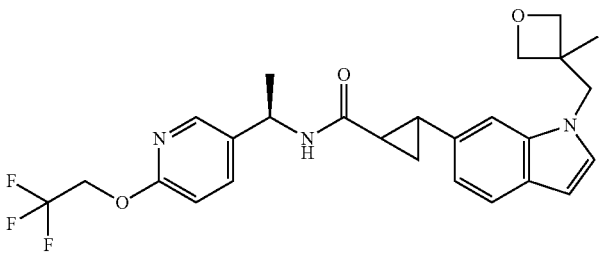
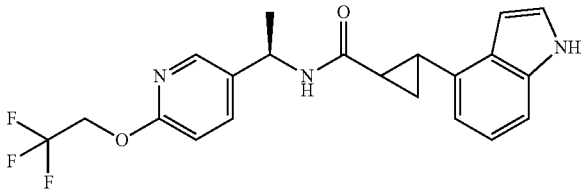
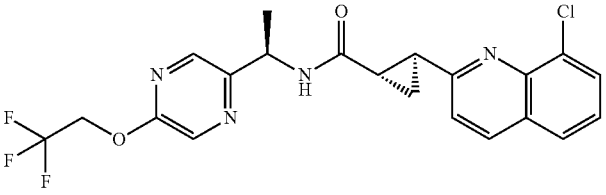
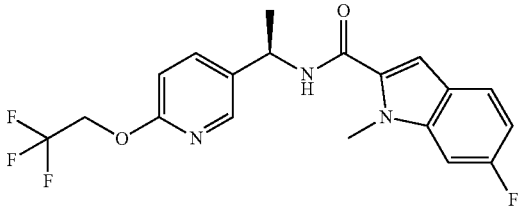
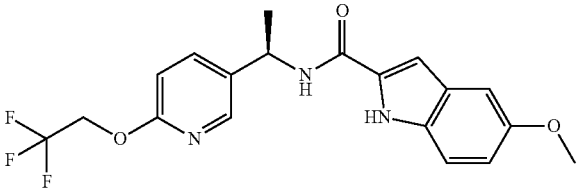
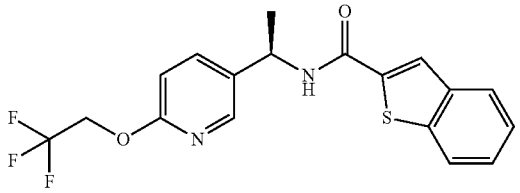
Example 212	trans-2-(1H-indol-7-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 213	trans-2-(1-((3-methyloxetan-3-yl)methyl)-1H-indol-6-yl)-N-((R)-1-(6-(2,2,2-trifluoro-ethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 214	trans-2-(1H-indol-4-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 215	(1S*,2S*)-2-(8-chloroquinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 216	(R)-6-fluoro-1-methyl-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-1H-indole-2-carboxamide	
Example 217	(R)-5-methoxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-1H-indole-2-carboxamide	
Example 218	(R)-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)benzo[b]thiophene-2-carboxamide	

TABLE 3-continued

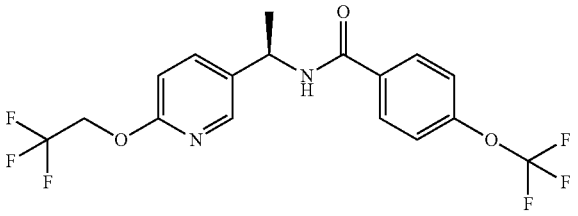
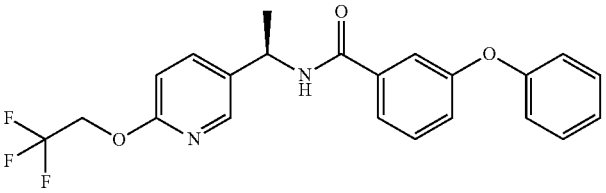
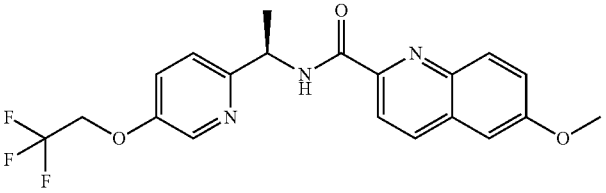
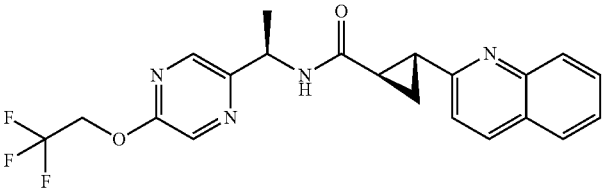
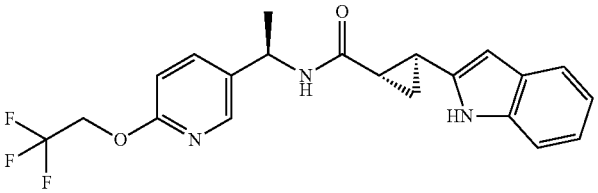
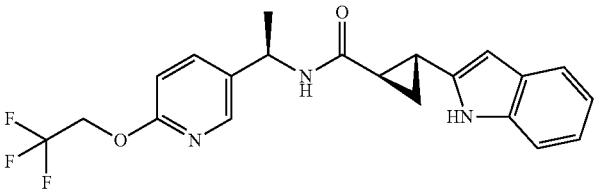
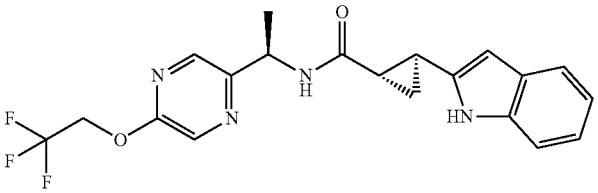
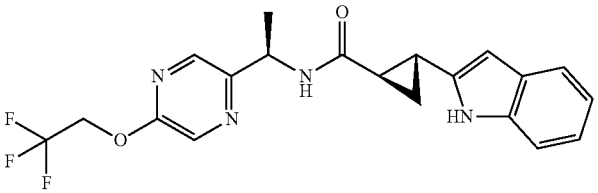
Example 219	(R)-N-(1-(6-(2,2,2-trifluoroethoxy) pyridin-3-yl)ethyl)-4-(trifluoromethoxy)benzamide	
Example 220	(R)-3-phenoxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)benzamide	
Example 221	(R)-6-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)quinoline-2-carboxamide	
Example 222	(1R*,2R*)-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 223	(1S*,2S*)-2-(1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 224	(1R*,2R*)-2-(1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 225	(1S*,2S*)-2-(1H-indol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 226	(1R*,2R*)-2-(1H-indol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

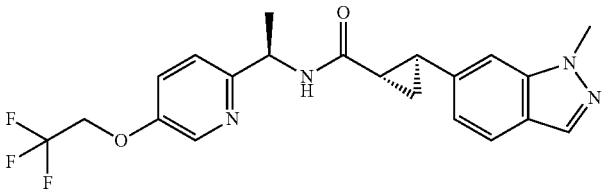
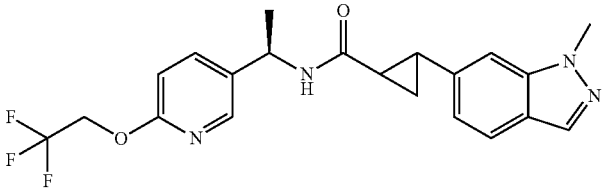
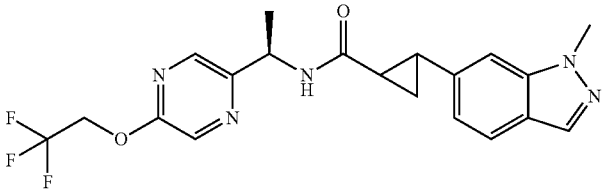
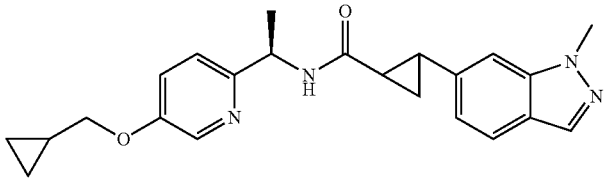
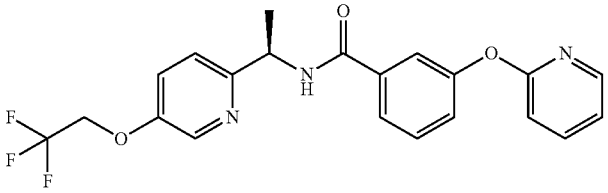
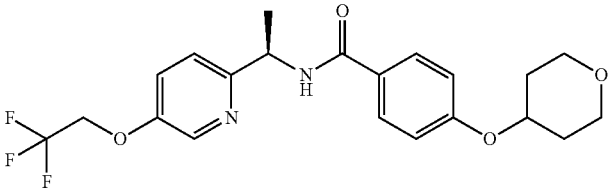
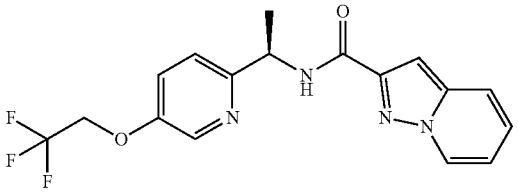
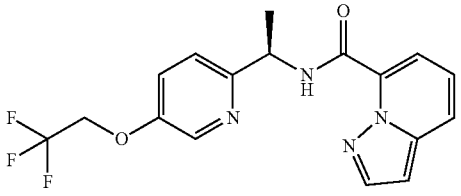
Example 227	(1S*,2S*)-2-(1-methyl-1H-indazol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 228	trans-2-(1-methyl-1H-indazol-6-yl)-N-((R)-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 229	trans-2-(1-methyl-1H-indazol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxemide	
Example 230	trans-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(1-methyl-1H-indazol-6-yl)cyclopropanecarboxamide	
Example 231	(R)-3-(pyridin-2-yloxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 232	(R)-4-(tetrahydro-2H-pyran-4-yloxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 233	(R)-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)pyrazolo[1,5-a] pyridine-2-carboxamide	
Example 234	(R)-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)pyrazolo[1,5-a] pyridine-7-carboxamide	

TABLE 3-continued

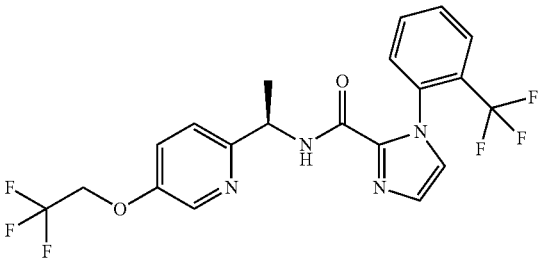
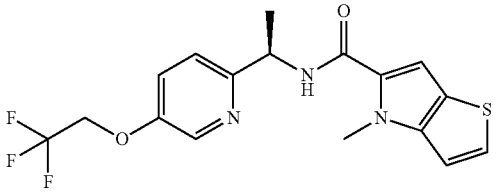
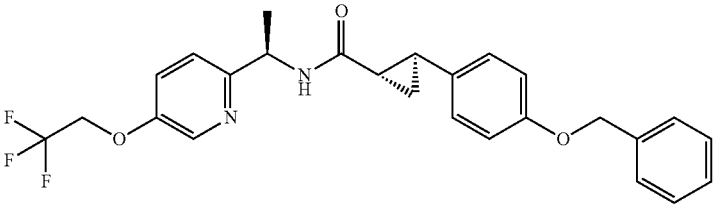
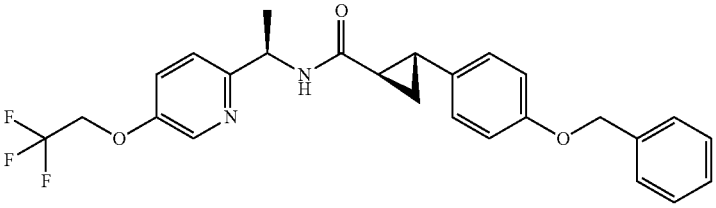
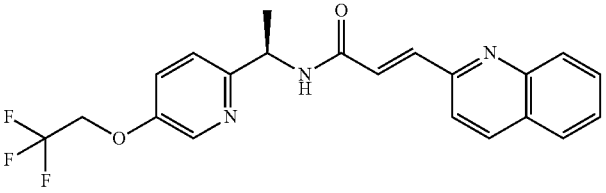
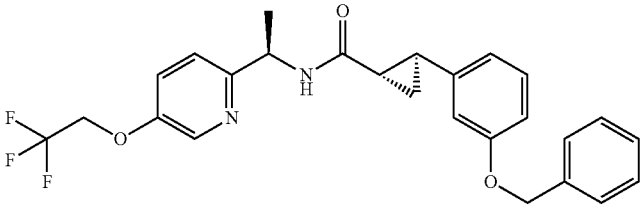
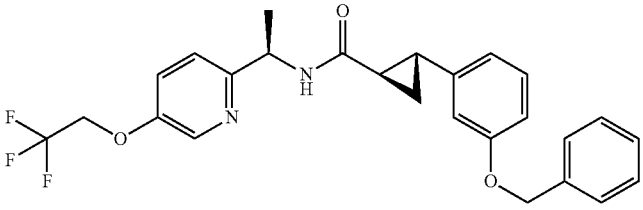
Example 235	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1-(2-(trifluoromethyl)phenyl)-1H-imidazole-2-carboxamide	
Example 236	(R)-4-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide	
Example 237	(1S*,2S*)-2-(4-(benzyloxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 238	(1R*,2R*)-2-(4-(benzyloxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 239	(R,E)-3-(quinolin-2-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acrylamide	
Example 240	(1S*,2S*)-2-(3-(benzyloxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 241	(1R*,2R*)-2-(3-(benzyloxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

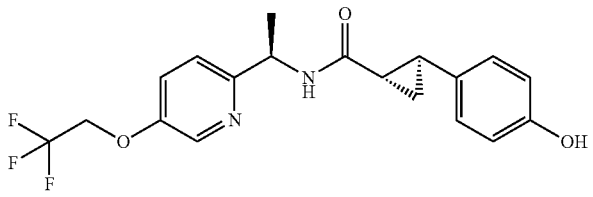
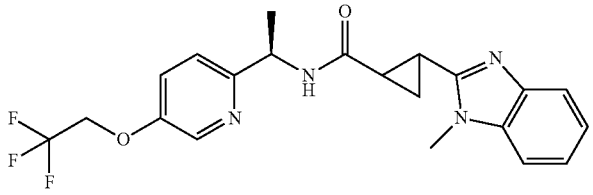
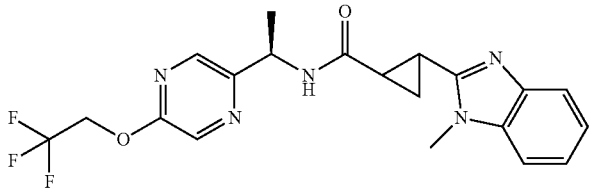
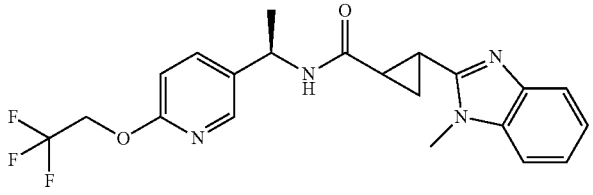
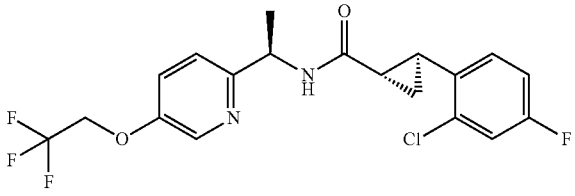
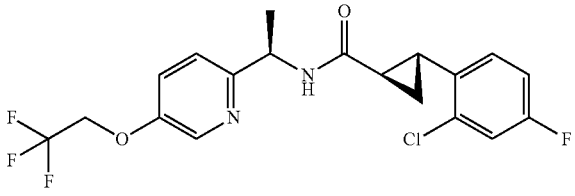
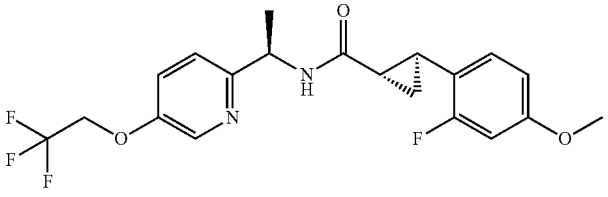
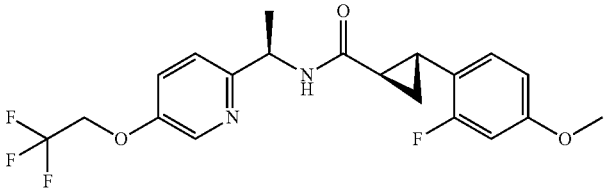
Example 242	(1S*,2S*)-2-(4-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 243	trans-2-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 244	trans-2-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 245	trans-2-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 246	(1S*,2S*)-2-(2-chloro-4-fluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 247	(1R*,2R*)-2-(2-chloro-4-fluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 248	(1S*,2S*)-2-(2-fluoro-4-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 249	(1R*,2R*)-2-(2-fluoro-4-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

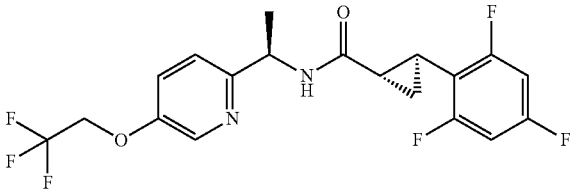
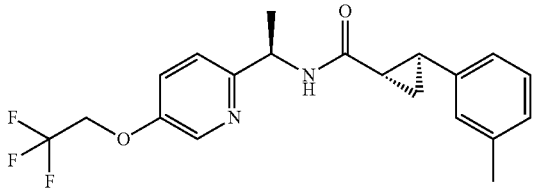
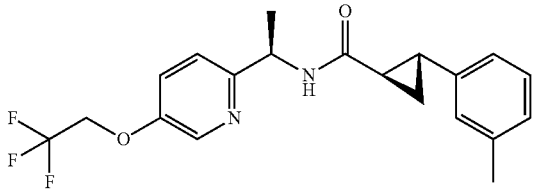
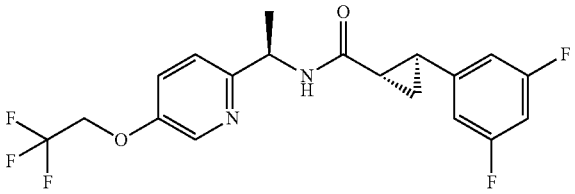
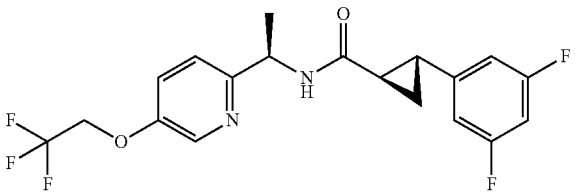
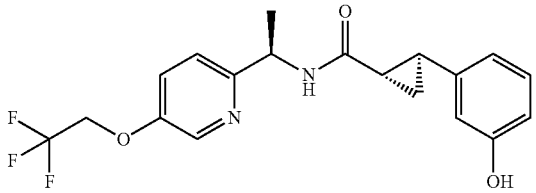
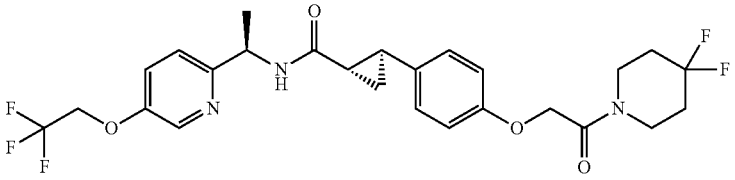
Example 250	(1S*,2S*)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl) cyclopropanecarboxamide	
Example 251	(1S*,2S*)-2-m-tolyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 252	(1R*,2R*)-2-m-talyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 253	(1S*,2S*)-2-(3,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 254	(1R*,2R*)-2-(3,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 255	(1S*,2S*)-2-(3-hydroxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 256	(1S*,2S*)-2-(4-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

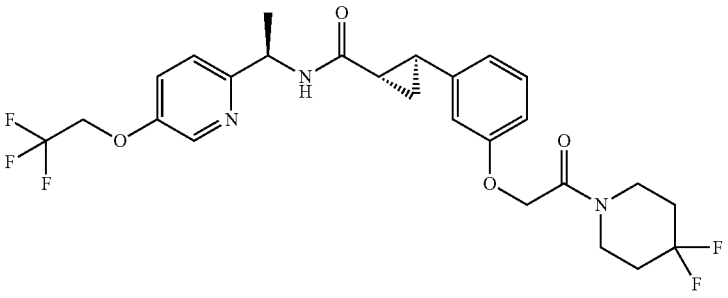
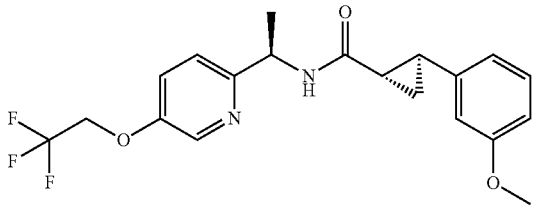
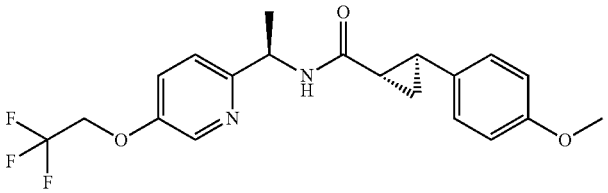
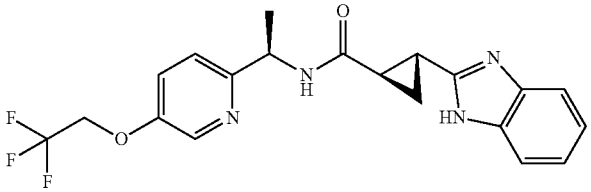
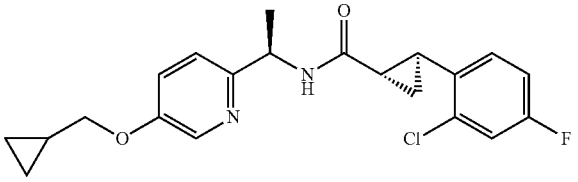
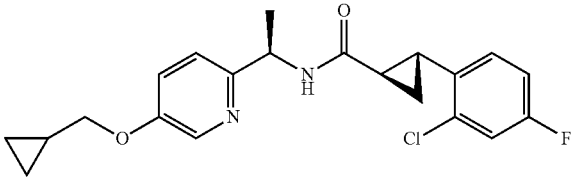
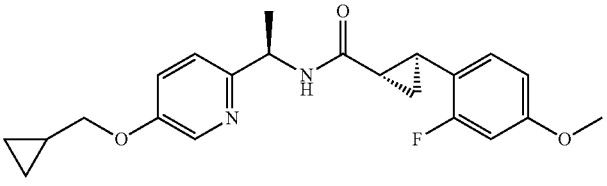
Example 257	(1S*,2S*)-2-(3-(2-(4,4-difluoropiperidin-1-yl)-2-oxoethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 258	(1S*,2S*)-2-(3-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 259	(1S*,2S*)-2-(4-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 260	(1R*,2R*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 261	(1S*,2S*)-2-(2-chloro-4-fluorophenyl)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 262	(1S*,2S*)-2-(2-chloro-4-fluorophenyl)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 263	(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(2-fluoro-4-methoxyphenyl)cyclopropanecarboxamide	

TABLE 3-continued

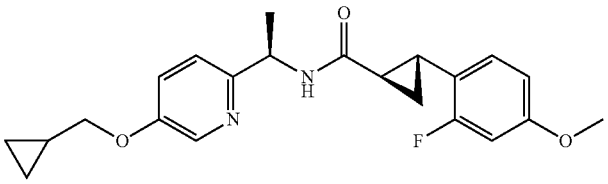
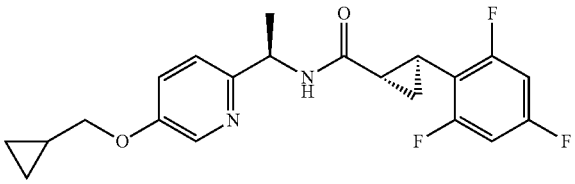
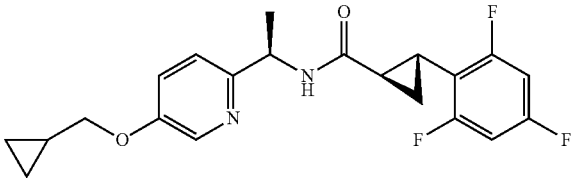
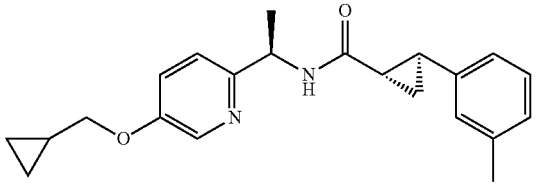
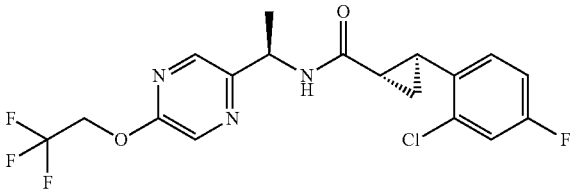
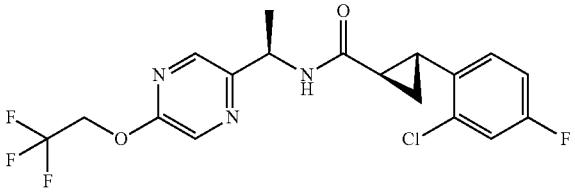
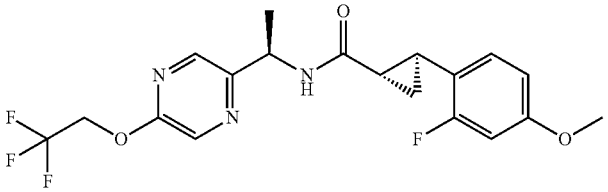
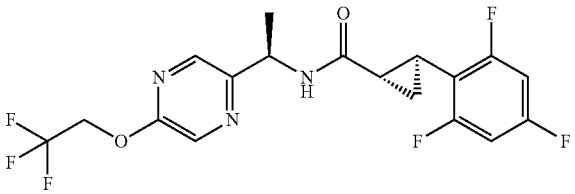
Example 264	(1R*,2R*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(2-fluoro-4-methoxy-phenyl)cyclopropanecarboxamide	
Example 265	(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl) cyclopropanecarboxamide	
Example 266	(1R*,2R*)-N-((R)-1-(5-(cyclopropylethoxy) pyridin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl) cyclopropanecarboxamide	
Example 267	(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-2-m-tolylcyclopropanecarboxamide	
Example 268	(1S*,2S*)-2-(2-chloro-4-fluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 269	(1R*,2R*)-2-(2-chloro-4-fluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 270	(1S*,2S*)-2-(2-fluoro-4-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 271	(1S*,2S*)-N-((R)-1-(5-(2,2,2-trifluoroethoxy) pyrazin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl) cyclopropanecarboxamide	

TABLE 3-continued

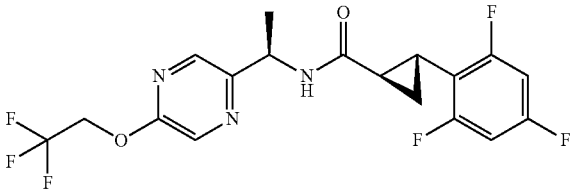
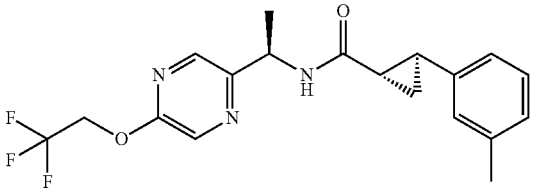
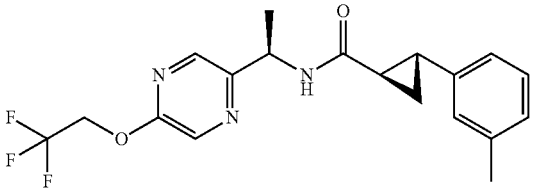
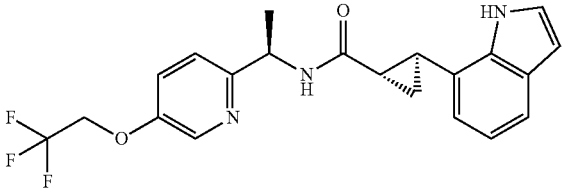
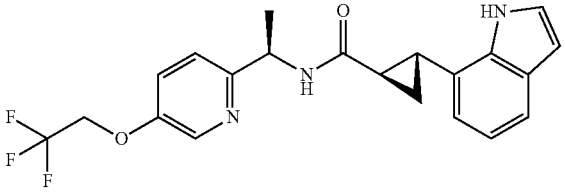
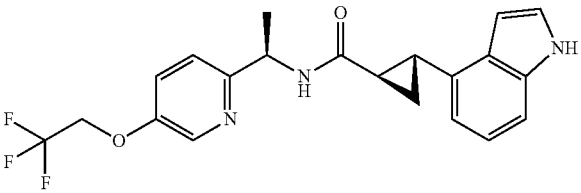
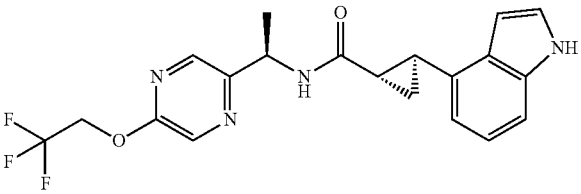
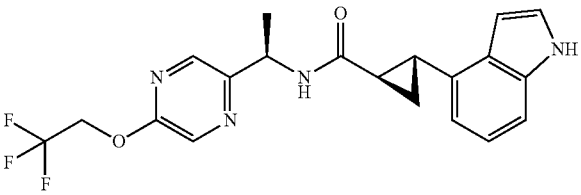
Example 272	(1R*,2R*)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl) cyclopropanecarboxamide	
Example 273	(1S*,2S*)-2-m-tolyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 274	(1R*,2R*)-2-m-tolyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 275	(1S*,2S*)-2-(1H-indol-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 276	(1R*,2R*)-2-(1H-indol-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 277	(1R*,2R*)-2-(1H-indol-4-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 278	(1S*,2S*)-2-(1H-indol-4-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 279	(1R*,2R*)-2-(1H-Indol-4-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

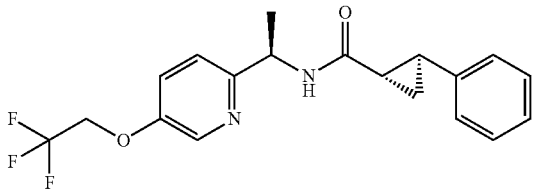
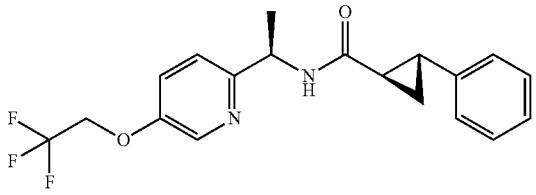
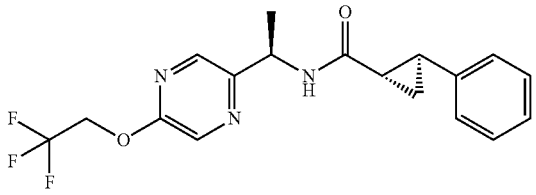
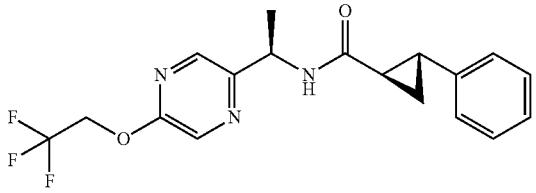
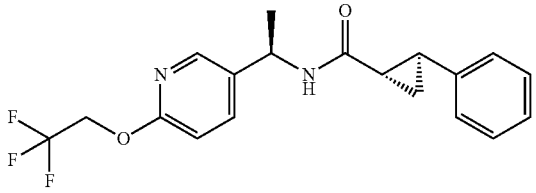
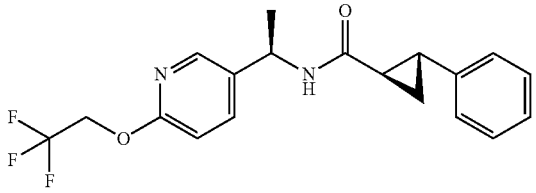
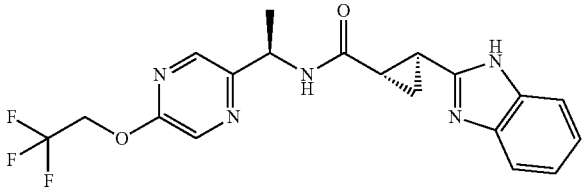
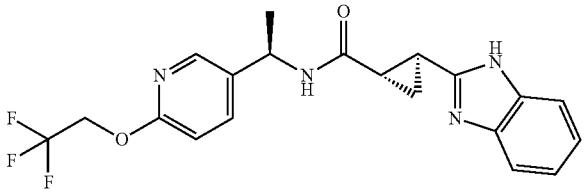
Example 280	(1S*,2S*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 281	(1R*,2R*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 282	(1S*,2S*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 283	(1R*,2R*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 284	(1S*,2S*)-2-phenyl-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 285	(1R*,2R*)-2-phenyl-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 286	(1S*,2S*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 287	(1S*,2S*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

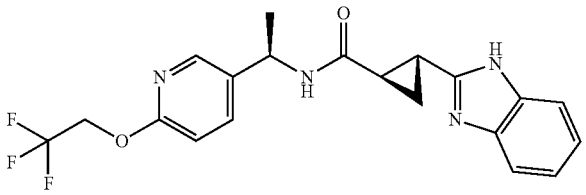
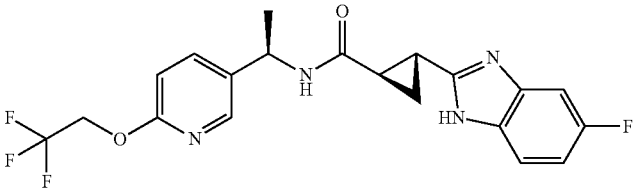
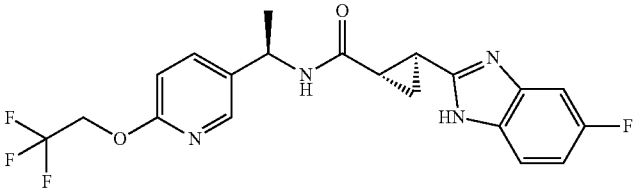
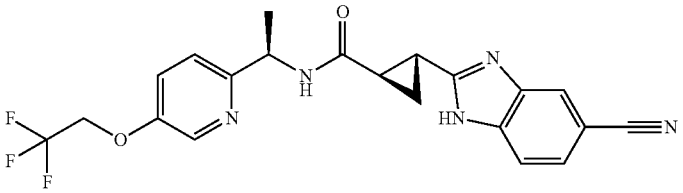
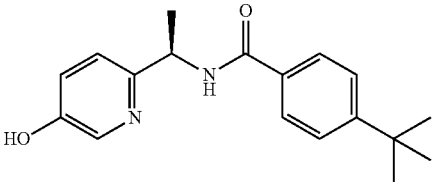
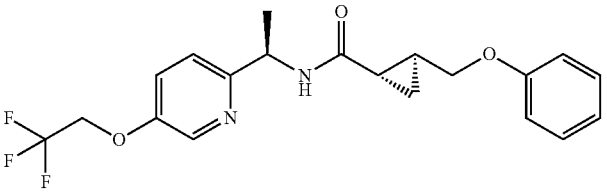
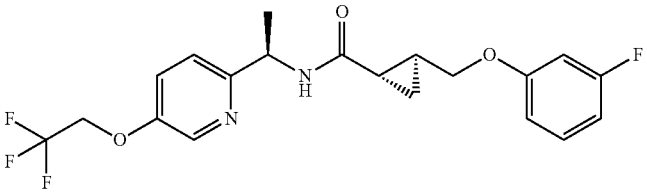
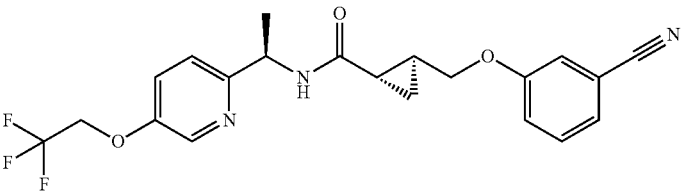
Example 288	(1R*,2R*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 289	(1R*,2R*)-2-(5-fluoro-1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl) cyclopropanecarboxamide	
Example 290	(1S*,2S*)-2-(5-fluoro-1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoro-ethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 291	(1R*,2R*)-2-(5-cyano-1H-benzo[d]imidazol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 292	(R)-4-tert-butyl-N-(1-(5-hydroxy-pyridin-2-yl)ethyl)benzamide	
Example 293	(1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 294	(1S*,2S*)-2-((3-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 295	(1S*,2S*)-2-((3-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanacarboxamide	

TABLE 3-continued

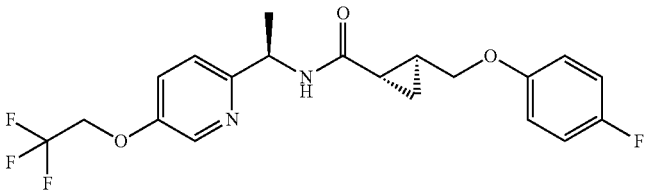
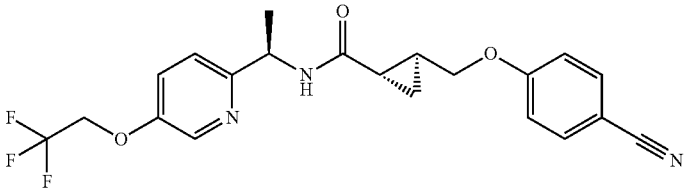
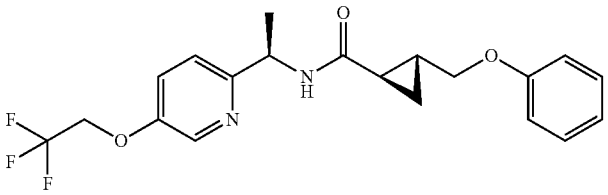
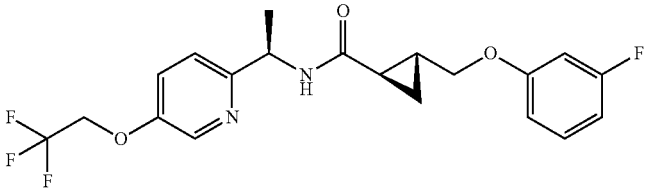
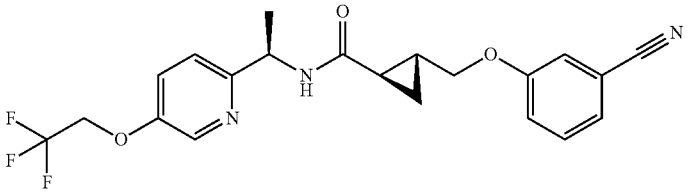
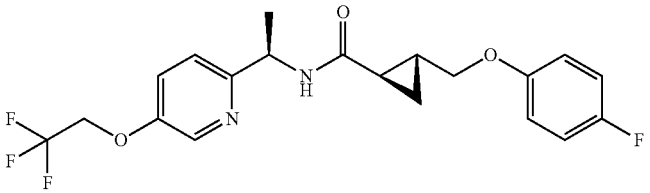
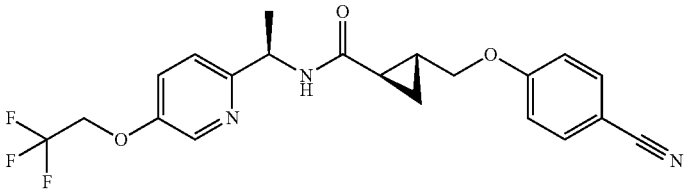
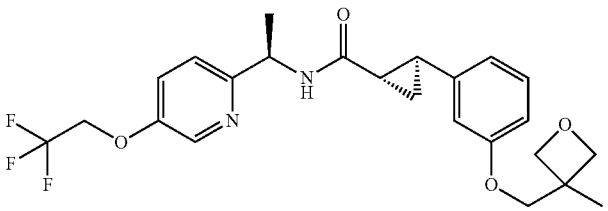
Example 296	(1S*,2S*)-2-((4-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 297	(1S*,2S*)-2-((4-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 298	(1R*,2R*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Exemple 299	(1R*,2R*)-2-((3-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluomethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 300	(1R*,2R*)-2-((3-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 301	(1R*,2R*)-2-((4-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 302	(1R*,2R*)-2-((4-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 303	(1S*,2S*)-2-(3-((3-methyloxetan-3-yl)methoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

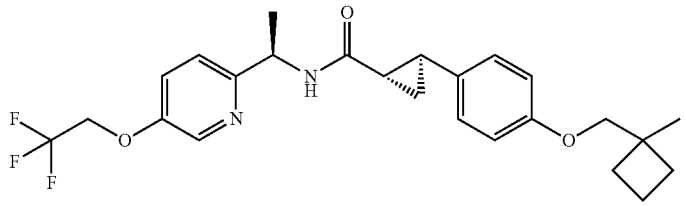
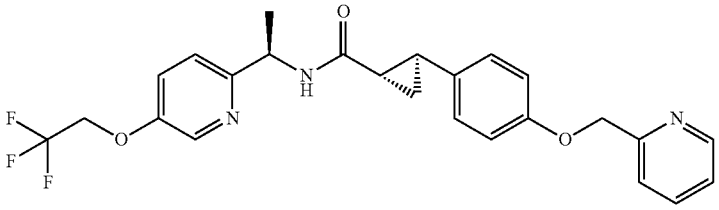
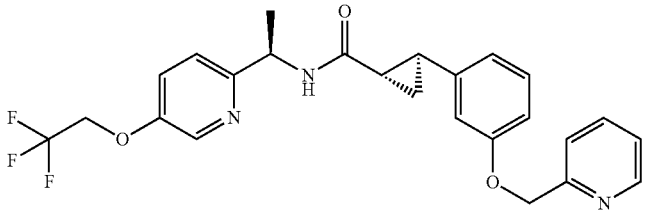
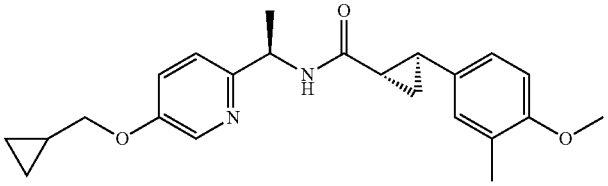
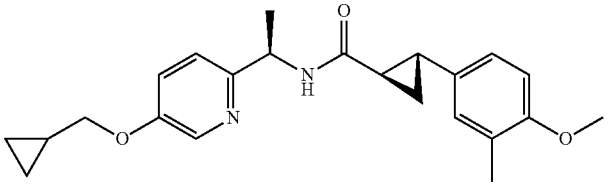
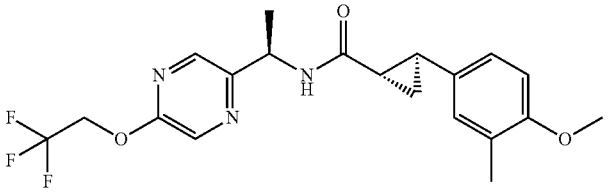
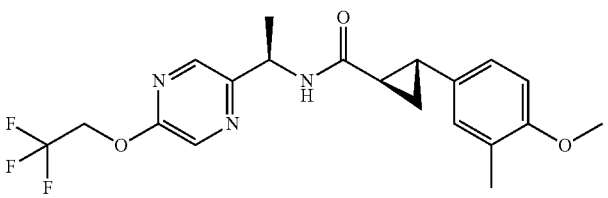
Example 304	(1S*,2S*)-2-(4-((3-methyloxetan-3-yl)methoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 305	(1S*,2S*)-2-(4-(pyridin-2-ylmethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 306	(1S*,2S*)-2-(3-(pyridin-2-ylmethoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 307	(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(4-methoxy-3-methylphenyl) cyclopropanecarboxamide	
Example 308	(1R*,2R*)-N-((R)-1-(5-(cyclopropylmethoxy) pyridin-2-yl)ethyl)-2-(4-methoxy-3-methylphenyl) cyclopropanecarboxamide	
Example 309	(1S*,2S*)-2-(4-methoxy-3-methylphenyl)-N-((R)-1-(5-(2,2,2-trifluomethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 310	(1R*,2R*)-2-(4-methoxy-3-methylphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

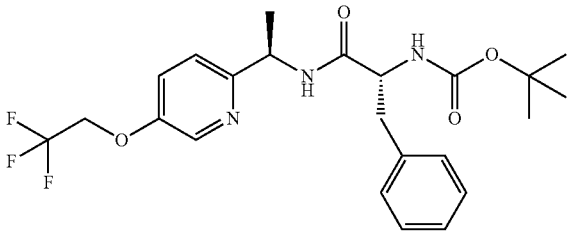
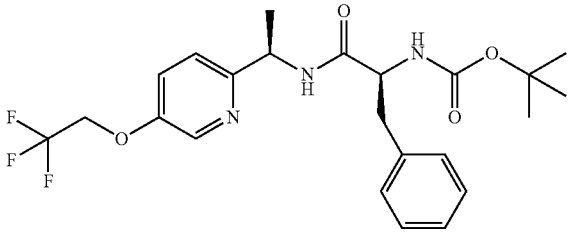
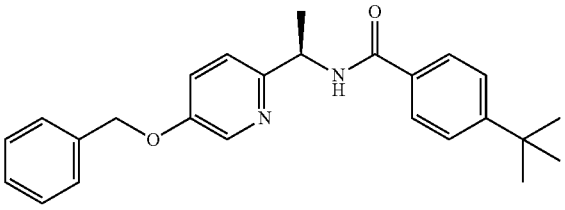
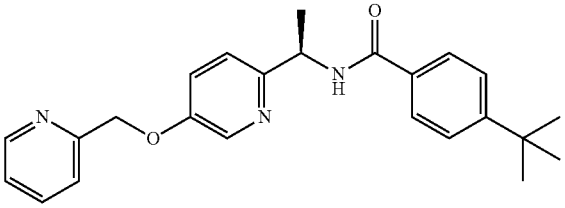
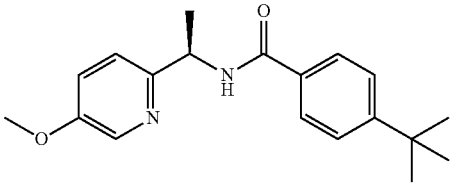
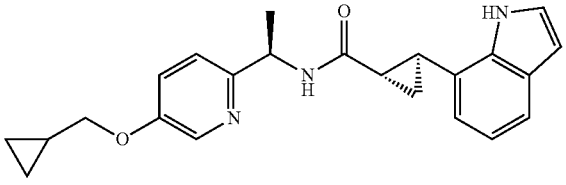
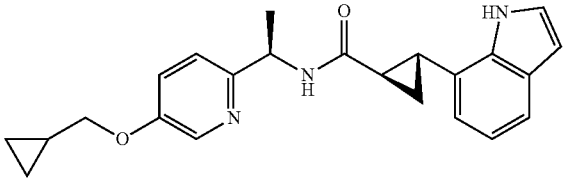
Example 311	tert-butyl (R)-1-oxo-3-phenyl-1-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethylamino)propan-2-ylcarbamate	
Example 312	tert-butyl (S)-1-oxo-3-phenyl-1-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethylamino)propan-2-ylcarbamate	
Example 313	(R)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-4-tert-butylbenzamide	
Example 314	(R)-4-tert-butyl-N-(1-(5-(pyridin-2-yl-methoxy)pyridin-2-yl)ethyl)benzamide	
Example 315	(R)-4-tert-butyl-N-(1-(5-methoxypyridin-2-yl)ethyl)benzamide	
Example 316	(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(1H-indol-7-yl)cyclopropanecarboxamide	
Example 317	(1R*,2R*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(1H-indol-7-yl)cyclopropanecarboxamide	

TABLE 3-continued

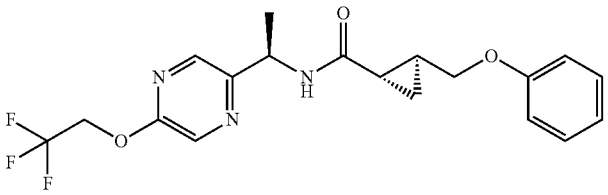
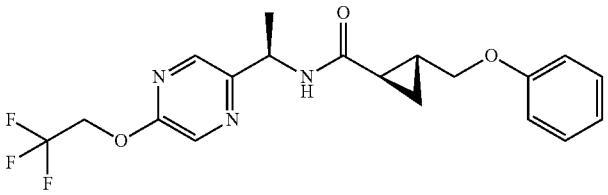
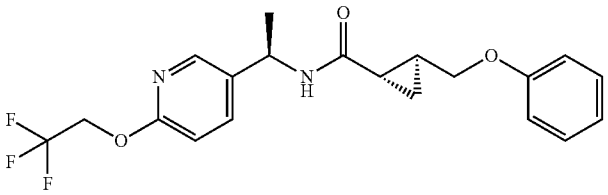
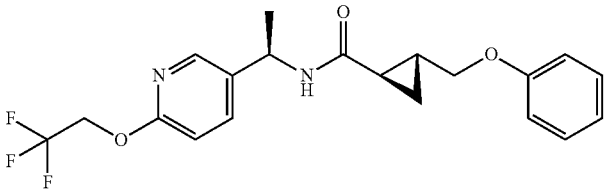
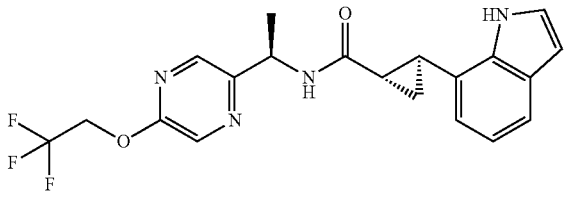
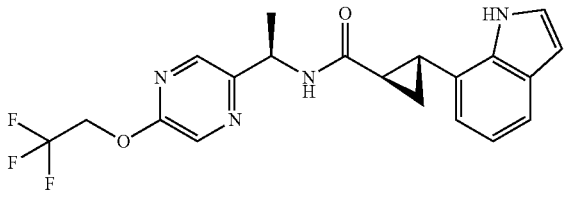
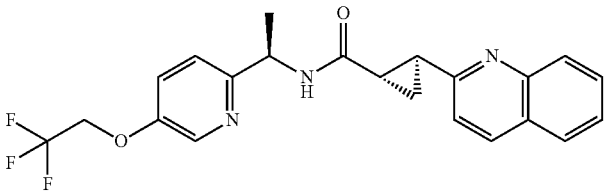
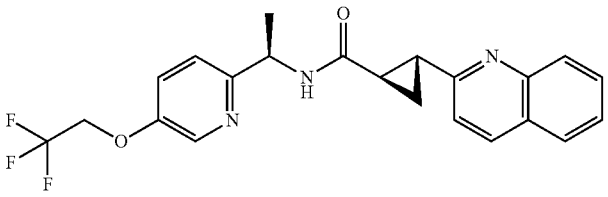
Example 318	(1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 319	(1R*,2R*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 320	(1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Example 321	(1R*,2R*)-2-(phenoxymethyl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide	
Exemple 322	(1S*,2S*)-2-(1H-indol-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 323	(1R*,2R*)-2-(1H-indol-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 324	(1S*,2S*)-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 325	(1R*,2R*)-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

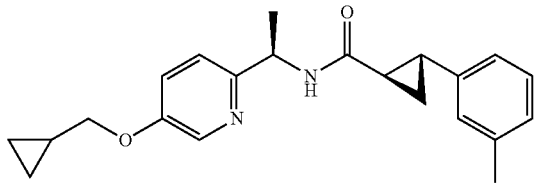
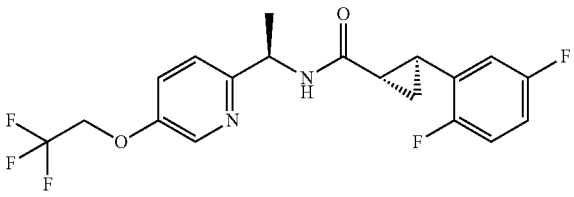
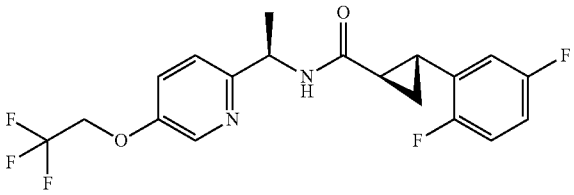
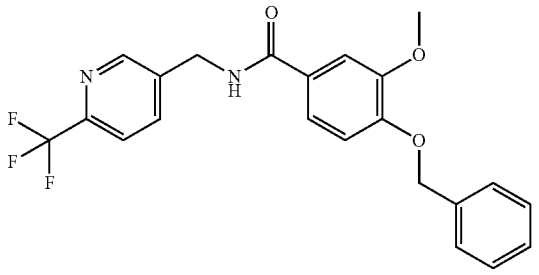
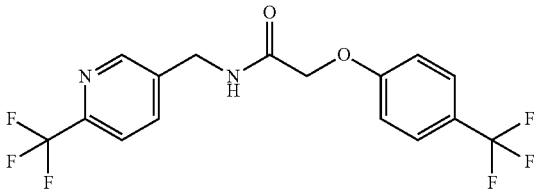
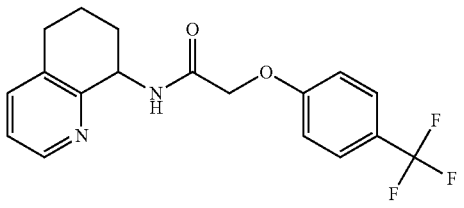
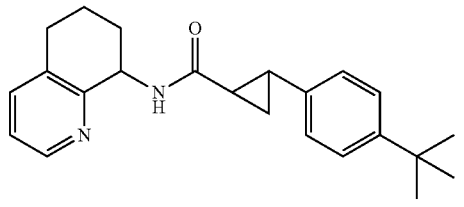
Example 326	(1R*,2R*)-N-((R)-1-(5-(cyclopropyl-methoxy)pyridin-2-yl)ethyl)-2-m-tolylcyclopropanecarboxamide	
Example 327	(1S*,2S*)-2-(2,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 328	(1R*,2R*)-2-(2,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 329	4-(benzyloxy)-3-methoxy-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)benzamide	
Example 330	2-(4-(trifluoromethyl)phenoxy)-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide	
Example 331	N-(5,6,7,8-tetrahydroquinolin-8-yl)-2-(4-(trifluoromethyl)phenoxy) acetamide	
Example 332	2-(4-(tert-butyl)phenyl)-N-(5,6,7,8-tetrahydroquinolin-8-yl)cyclopropanecarboxamide	

TABLE 3-continued

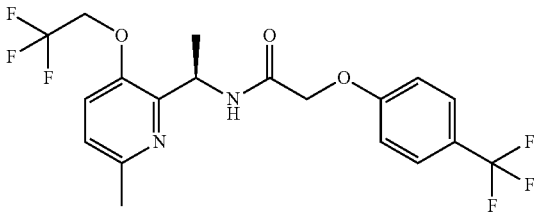
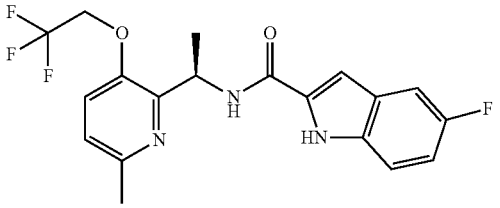
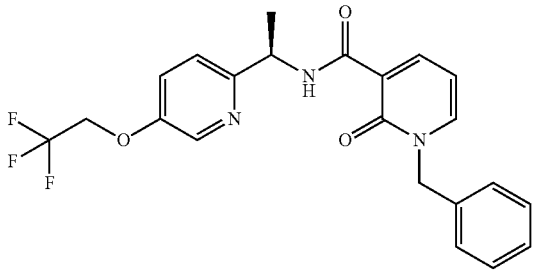
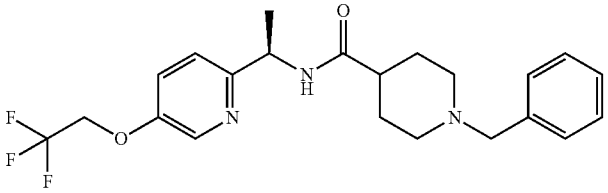
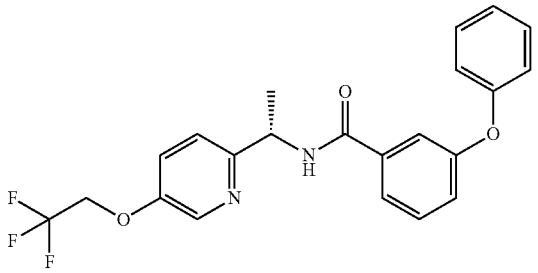
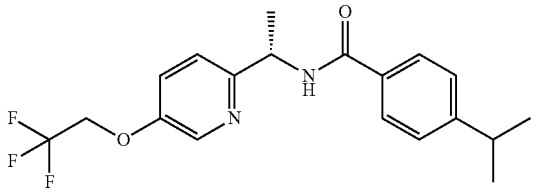
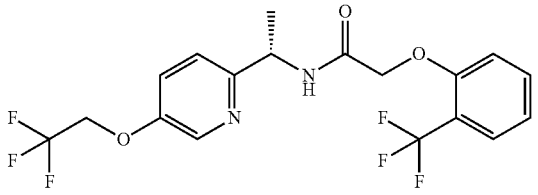
Example 333	(R)-N-(1-(6-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide	
Example 334	(R)-5-fluoro-N-(1-(8-methyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 335	(R)-1-benzyl-2-oxo-N-(1-(5-(2,2,2-trifluoro-ethoxy)pyridin-2-yl)ethyl)-1,2-dihydropyridine-3-carboxamide	
Example 336	(R)-1-benzyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)piperidine-4-carboxamide	
Example 337	(S)-3-phenoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 338	(S)-4-isopropyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 339	(S)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(2-(trifluoromethyl)phenoxy)acetamide	

TABLE 3-continued

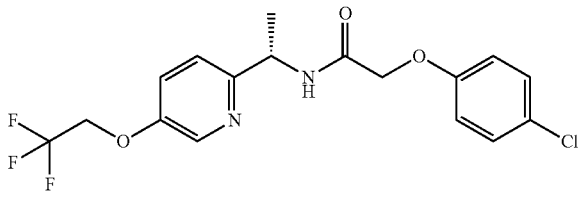
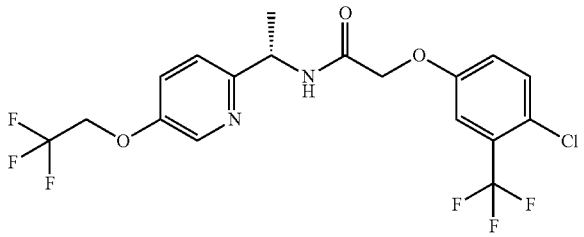
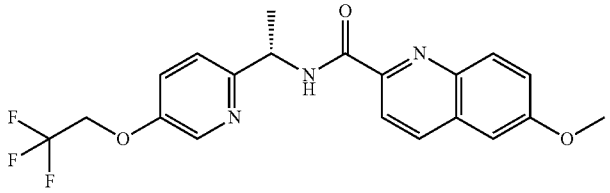
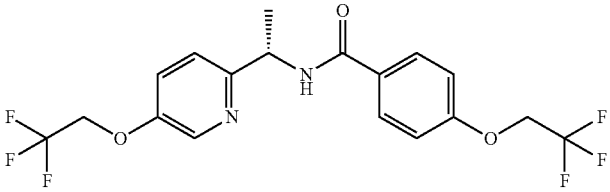
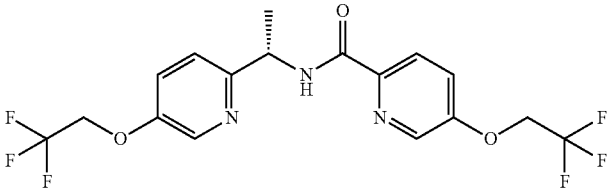
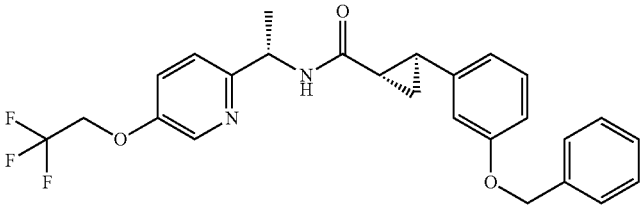
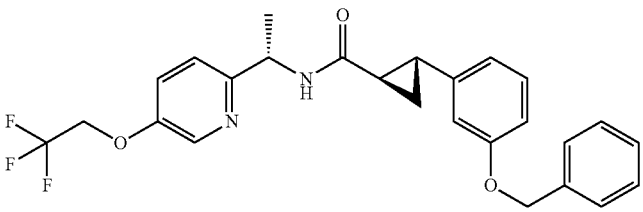
Example 340	(S)-2-(4-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 341	(S)-2-(4-chloro-3-(trifluoromethyl) phenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)acetamide	
Example 342	(S)-6-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)quinoline-2-carboxamide	
Example 343	(S)-4-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 344	(S)-5-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)picolinamide	
Example 345	(1S*,2S*)-2-(3-(benzyloxy)phenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 346	(1R*,2R*)-2-(3-(benzyloxy)phenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

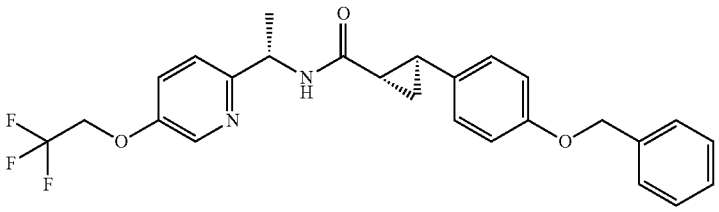
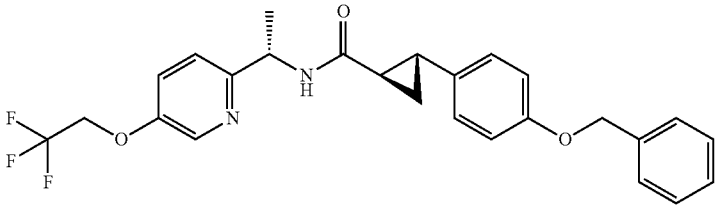
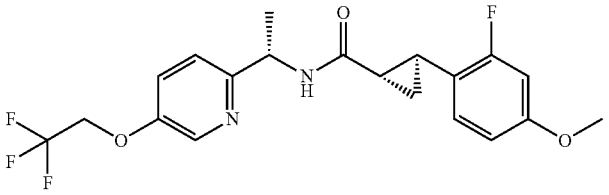
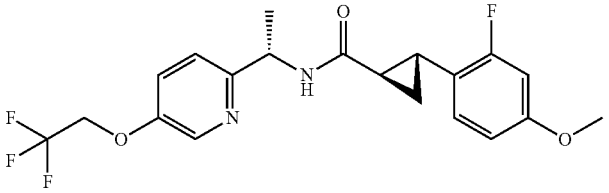
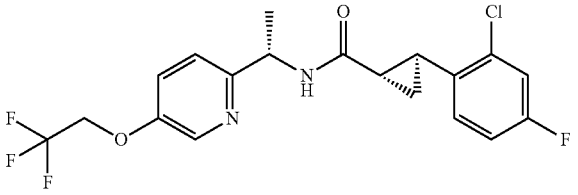
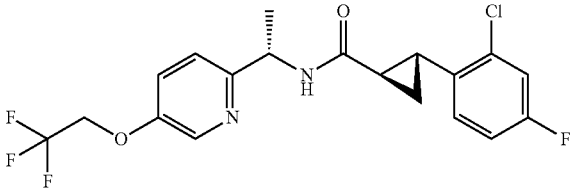
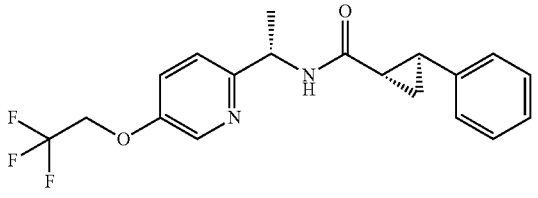
Example 347	(1S*,2S*)-2-(4-(benzyloxy)phenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 348	(1R*,2R*)-2-(4-(benzyloxy)phenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 349	(1S*,2S*)-2-(2-fluoro-4-methoxyphenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 350	(1R*,2R*)-2-(2-fluoro-4-methoxyphenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 351	(1S*,2S*)-2-(2-chloro-4-fluorophenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 352	(1R*,2R*)-2-(2-chloro-4-fluorophenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 353	(1S*,2S*)-2-phenyl-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	

TABLE 3-continued

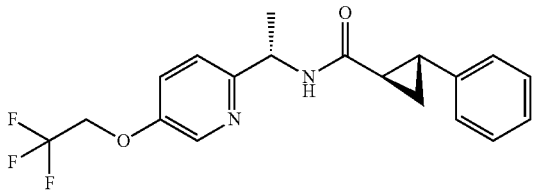
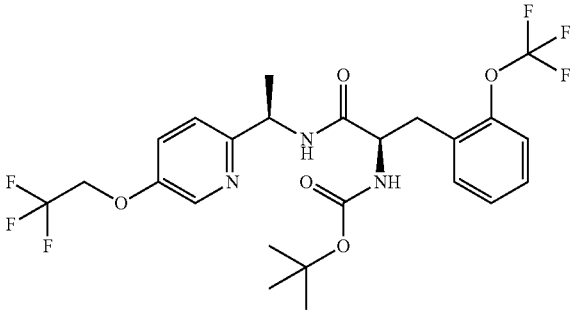
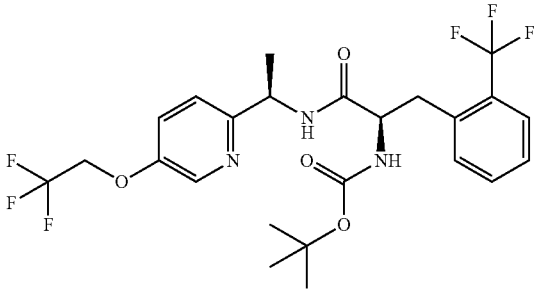
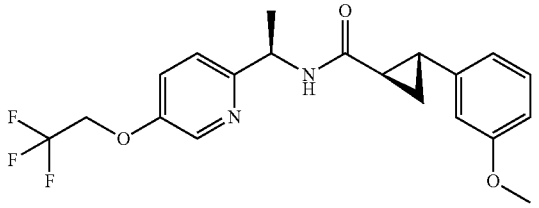
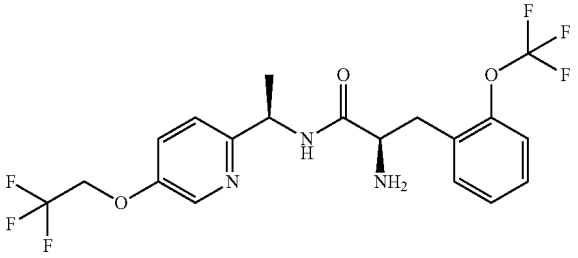
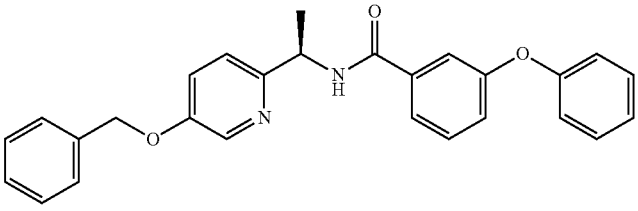
Example 354	(1R*,2R*)-2-phenyl-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 355	tert-butyl((R)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethoxy)phenyl)propan-2-yl)carbamate	
Example 356	tert-butyl ((R)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethyl)phenyl)propan-2-yl)carbamate	
Example 357	(1R*,2R*)-2-(3-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide	
Example 358	(R)-2-amino-N-((R)-1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)-3-(2-(trifluoromethoxy) phenyl)propanamide	
Example 359	(R)-N-(1-(5-(benzyloxy)pyridin-2-yl)ethyl)-3-phenoxybenzamide	

TABLE 3-continued

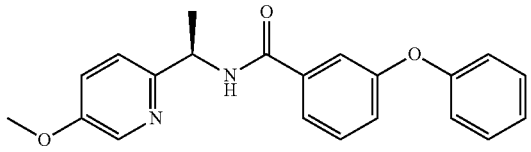
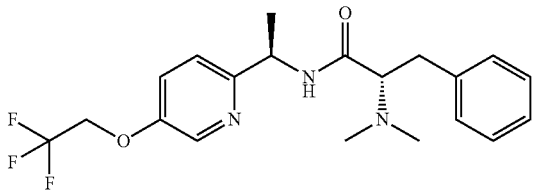
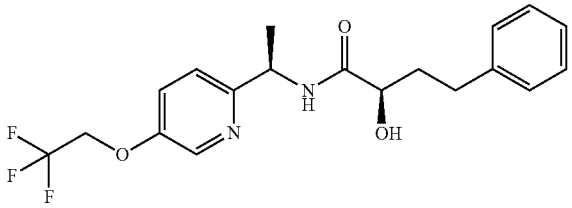
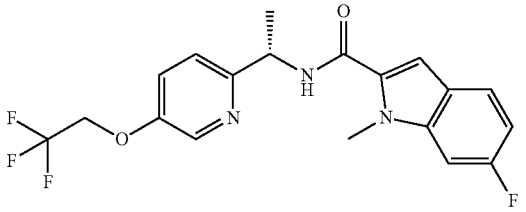
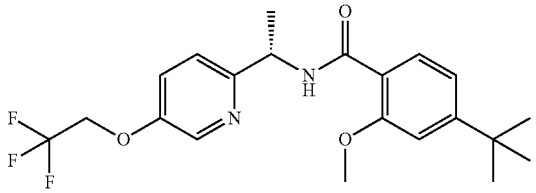
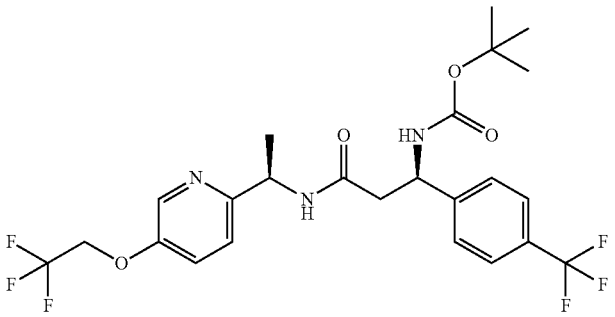
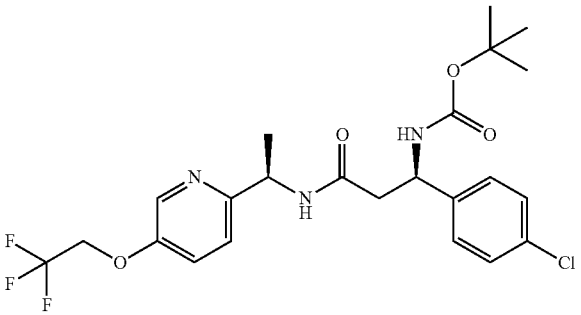
Example 360	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-3-phenoxybenzamide	
Example 361	(S)-2-(dimethylamino)-3-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	
Example 362	(R)-2-hydroxy-4-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)butanamide	
Example 363	(S)-6-fluoro-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 364	(S)-4-(tert-butyl)-2-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 365	tert-butyl ((S)-3-oxo-3-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-1-(4-(trifluoromethyl)phenyl)propyl)carbamate	
Example 366	tert-butyl ((S)-1-(4-chlorophenyl)-3-oxo-3-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propyl)carbamate	

TABLE 3-continued

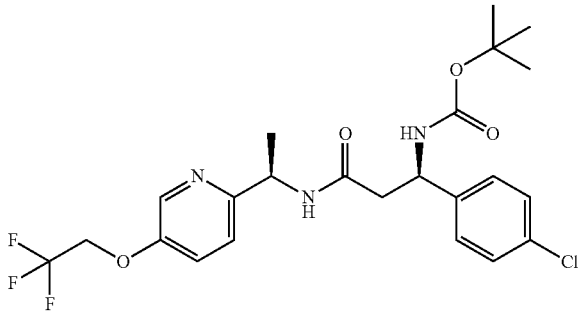
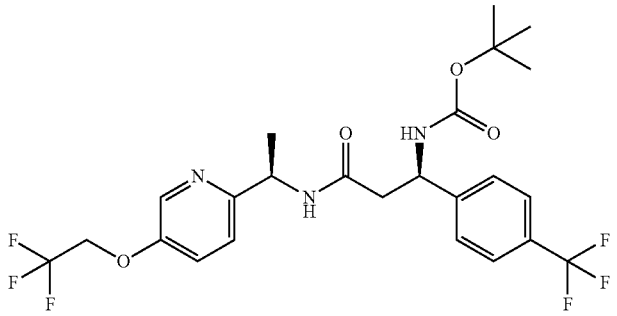
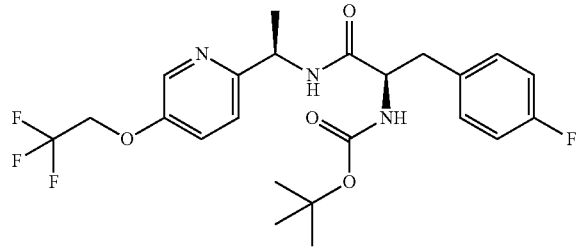
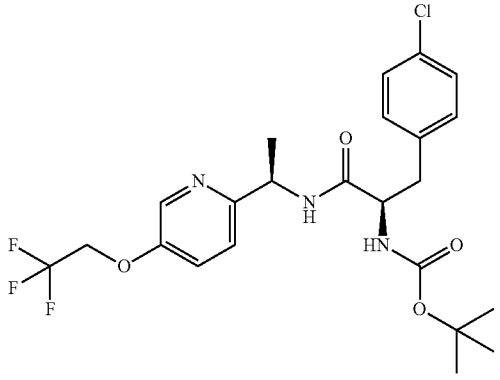
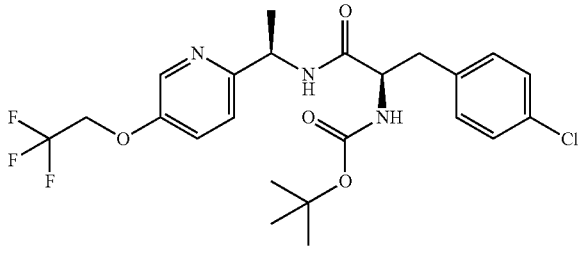
Example 367	tert-butyl ((R)-1-(4-chlorophenyl)-3-oxo-3-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propyl)carbamate	
Example 368	tert-butyl ((R)-3-oxo-3-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-1-(4-(trifluoromethyl)phenyl) propylcarbamate	
Example 369	tert-butyl ((3)-3-(4-fluorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate	
Example 370	tert-butyl ((S)-3-(4-chlorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate	
Example 371	tert-butyl ((R)-3-(4-chlorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate	

TABLE 3-continued

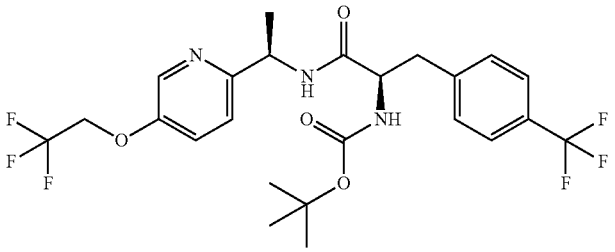
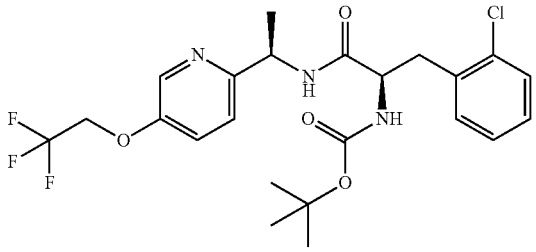
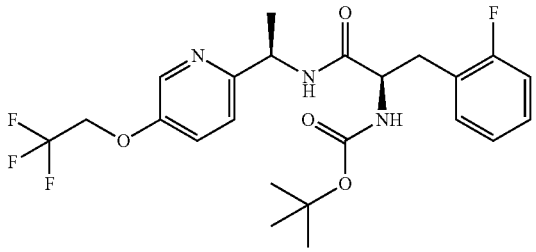
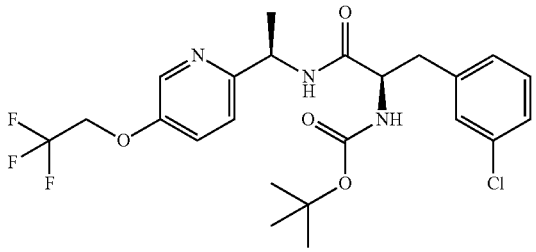
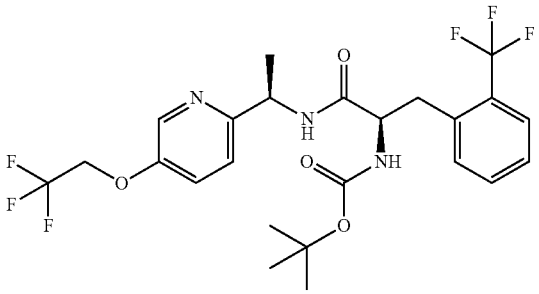
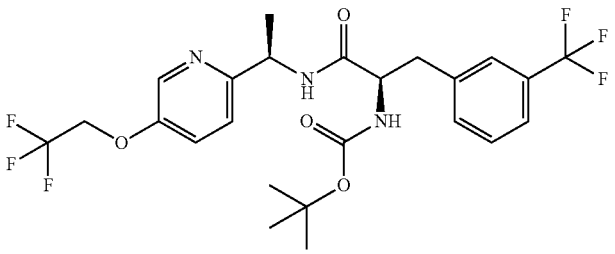
Example 372	tert-butyl ((S)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(4-(trifluoromethyl)phenyl) propan-2-yl)carbamate	
Example 373	tert-butyl ((S)-3-(2-chlorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate	
Example 374	tert-butyl((S)-3-(2-fluorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate	
Example 375	tert-butyl ((S)-3-(3-chlorophenyl)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)propan-2-yl)carbamate	
Example 376	tert-butyl ((3)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethyl)phenyl)propan-2-yl)carbamate	
Example 377	tert-butyl ((S)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)amino)-3-(3-(trifluoromethyl)phenyl)propan-2-yl)carbamate	

TABLE 3-continued

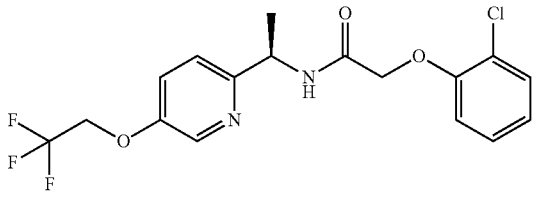
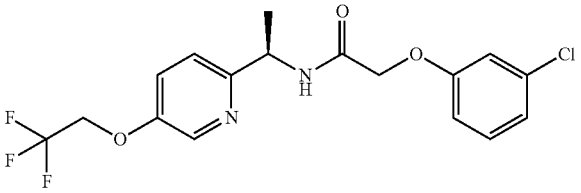
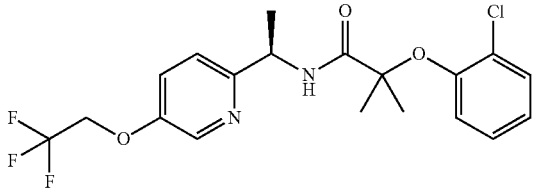
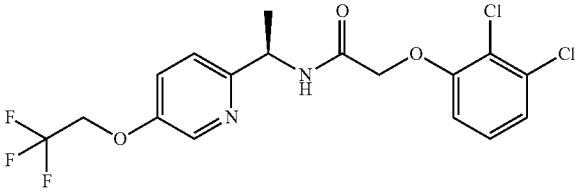
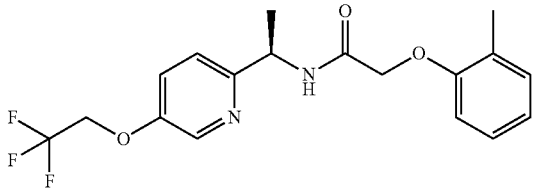
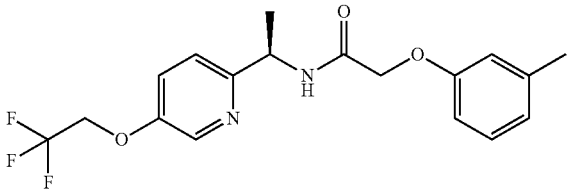
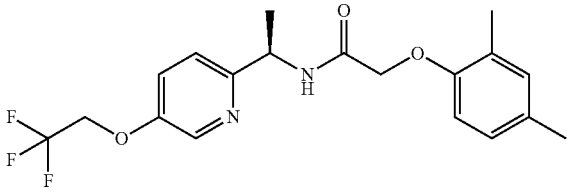
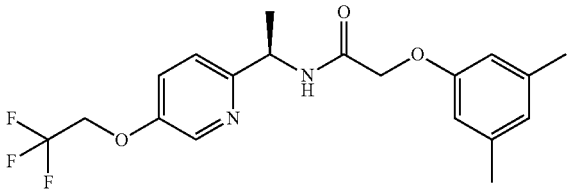
Example 378	(R)-2-(2-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 379	(R)-2-(3-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 380	(R)-2-(2-chlorophenoxy)-2-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	
Example 381	(R)-2-(2,3-dichlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 382	(R)-2-(o-tolyloxy)-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)acetamide	
Example 383	(R)-2-(m-tolyloxy)-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)acetamide	
Example 384	(R)-2-(2,4-dimethylphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 385	(R)-2-(3,5-dimethylphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	

TABLE 3-continued

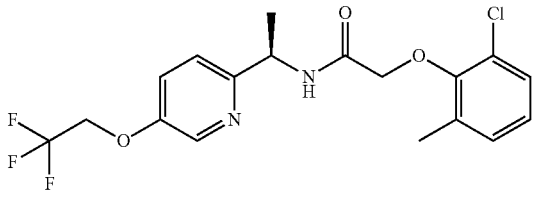
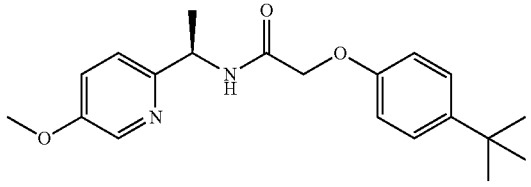
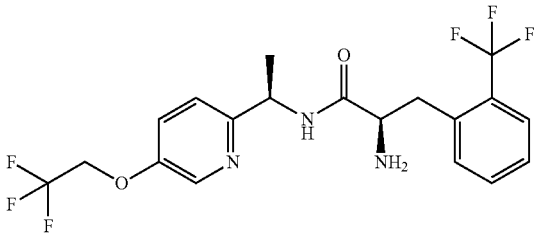
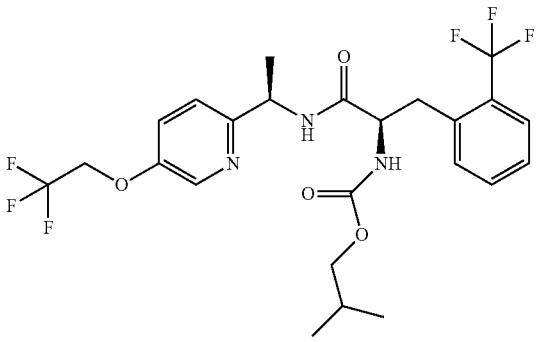
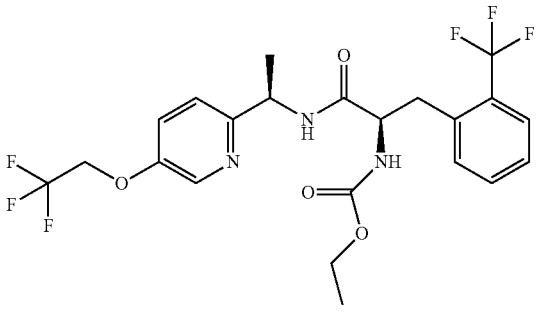
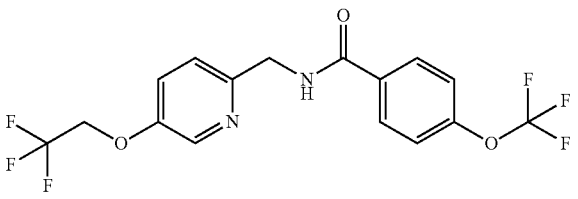
Example 386	(R)-2-(2-chloro-6-methylphenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 387	(R)-2-(4-(tert-butyl)phenoxy)-N-(1-(5-methoxypyridin-2-yl)ethyl)acetamide	
Example 388	(R)-2-amino-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(2-(trifluoromethyl)phenyl)propanamide	
Example 389	isobutyl ((R)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoro-ethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethyl)phenyl)propan-2-yl)carbamate	
Example 390	ethyl ((R)-1-oxo-1-(((R)-1-(5-(2,2,2-trifluoro-ethoxy)pyridin-2-yl)ethyl)amino)-3-(2-(trifluoromethyl)phenyl)propan-2-yl)carbamate	
Example 391	N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-4-(trifluoromethoxy)benzamide	

TABLE 3-continued

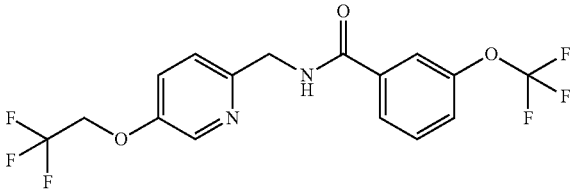
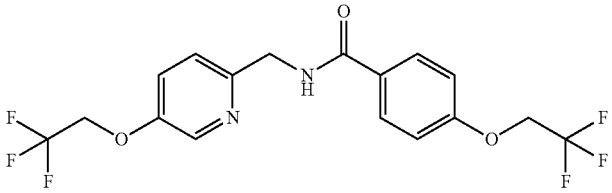
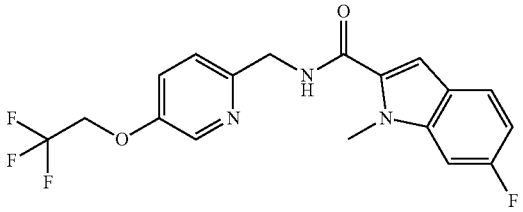
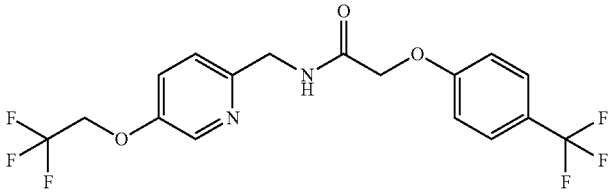
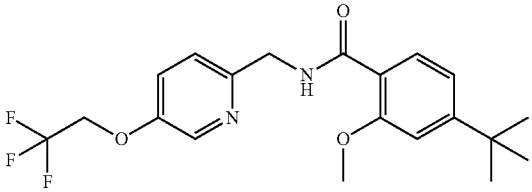
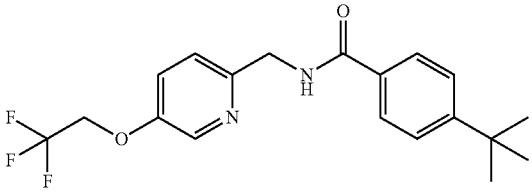
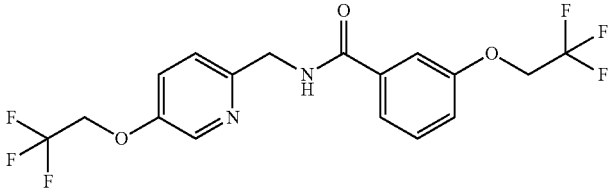
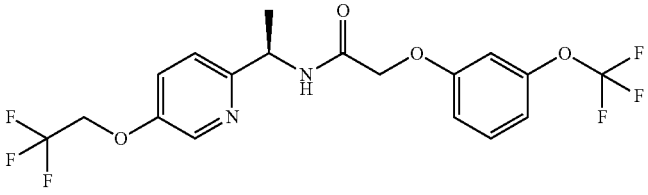
Example 392	N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-3-(trifluoromethoxy)benzamide	
Example 393	4-(2,2,2-trifluoroethoxy)-N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)benzamide	
Example 394	6-fluoro-1-methyl-N-((5-(2,2,2-trifluoroethoxy) pyridin-2-yl)methyl)-1H-indole-2-carboxamide	
Example 395	N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-2-(4-(trifluoromethyl)phenoxy)ecetamide	
Example 396	4-(tert-butyl)-2-methoxy-N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)benzamide	
Example 397	4-(tert-butyl)-N-((5-(2,2,2-trifluoroethoxy) pyridin-2-yl)methyl)benzamide	
Example 398	3-(2,2,2-trifluoroethoxy)-N-((5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)benzamide	
Example 399	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(3-(trifluoromethoxy)phenoxy) acetamide	

TABLE 3-continued

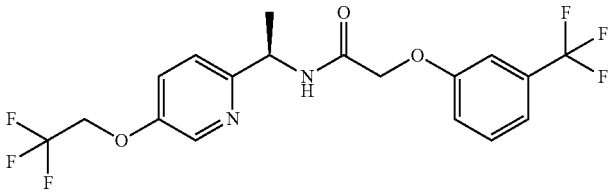
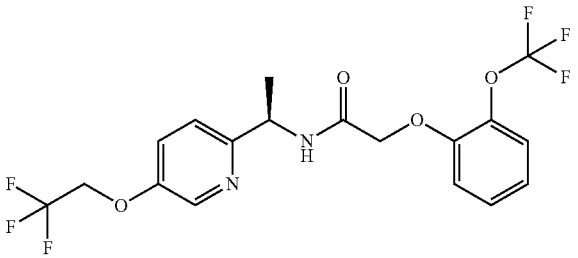
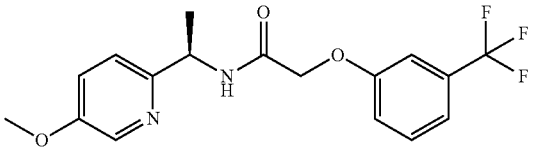
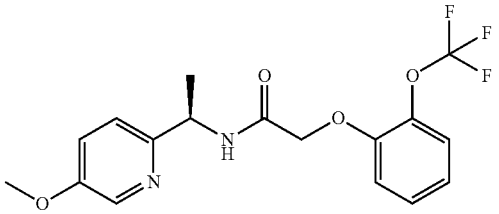
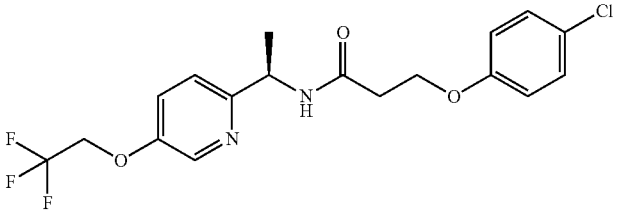
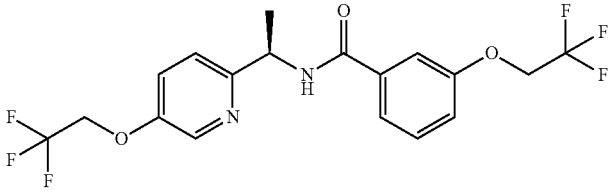
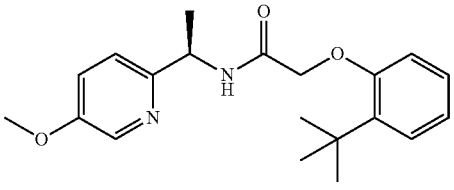
Example 400	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)phenoxy)acetamide	
Example 401	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(2-(trifluoromethoxy)phenoxy) acetamide	
Example 402	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)phenoxy)acetamide	
Example 403	(R)-N-(1-(5-methoxypyridin-2-yl) ethyl)-2-(2-(trifluoromethoxy) phenoxy)acetamide	
Example 404	(R)-3-(4-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)propanamide	
Example 405	(R)-3-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 406	(R)-2-(2-(tert-butyl)phenoxy)-N-(1-(5-methoxypyridin-2-yl)ethyl)acetemide	

TABLE 3-continued

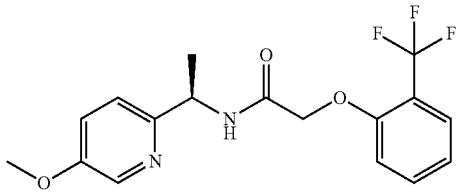
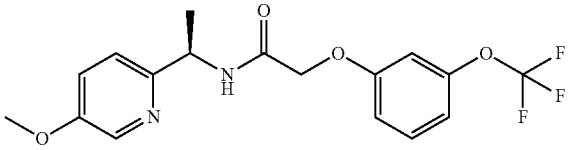
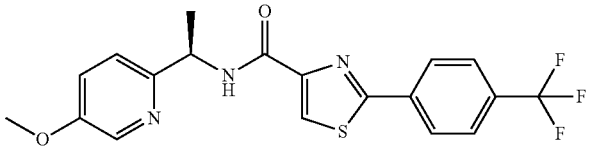
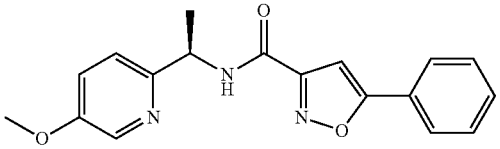
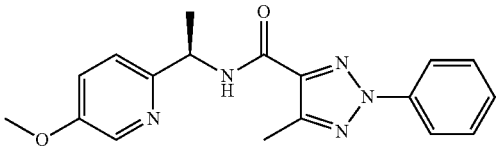
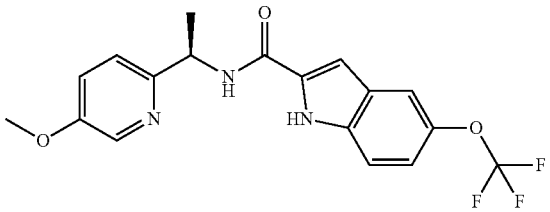
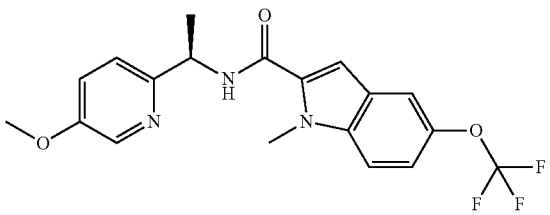
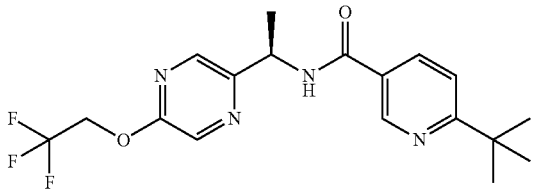
Example 407	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-2-(2-(trifluoromethyl)phenoxy)acetamide	
Example 408	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-2-(3-trifluoromethoxy)phenoxy) acetamide	
Example 409	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)thiazole-4-carboxamide	
Example 410	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-5-phenylisoxazole-3-carboxamide	
Example 411	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-5-methyl-2-phenyl-2H-1,2,3-triazole-4-carboxamide	
Example 412	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-5-(trifluoromethoxy)-1H-indole-2-carboxamide	
Example 413	(R)-N-(1-(5-methoxypyridin-2-yl)ethyl)-1-methyl-5-(trifluoromethoxy)-1H-indole-2-carboxamide	
Example 414	(R)-6-(tert-butyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)nicotinamide	

TABLE 3-continued

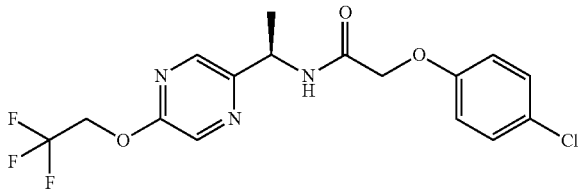
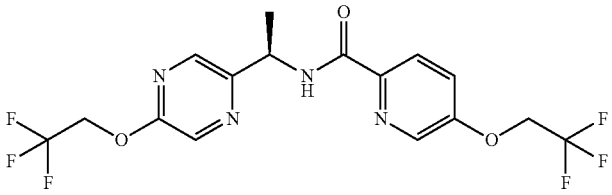
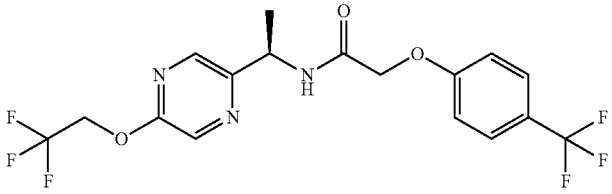
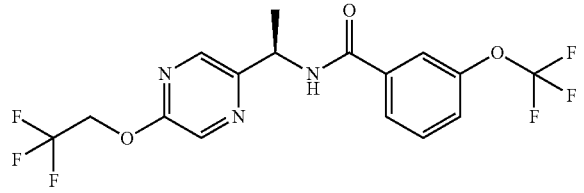
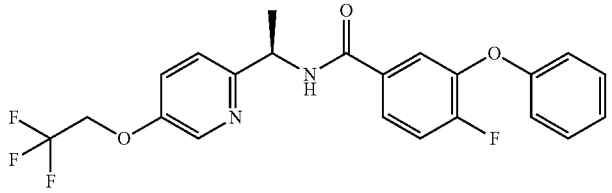
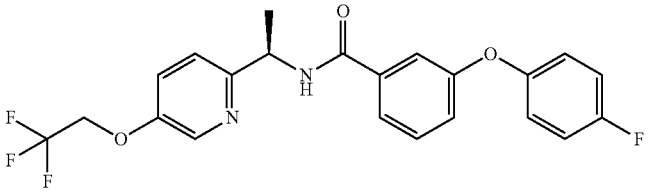
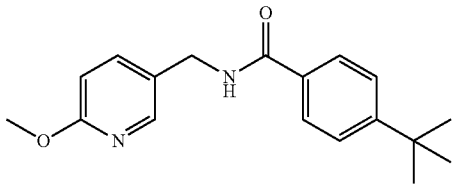
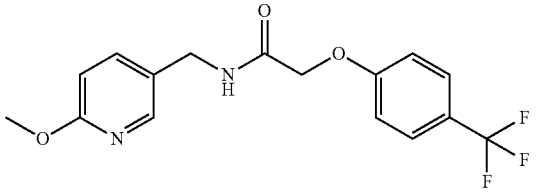
Example 415	(R)-2-(4-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)acetamide	
Example 416	(R)-5-(2,2,2-trifluoroethoxyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)picolinamide	
Example 417	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenoxy)acetamide	
Example 418	(R)-N-(1-(5-(2,2,2-trifluoroethoxy) pyrazin-2-yl)ethyl)-3-(trifluoromethoxy)benxamide	
Exemple 419	(R)-4-fluoro-3-phenoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Exemple 420	(R)-3-(4-fluorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 421	4-(tert-butyl)-N-((6-methoxypyridin-3-yl)methyl)benzamide	
Example 422	N-((6-methoxypyridin-3-yl)methyl)-2-(4-(trifluoromethyl)phenoxy)acetamide	

TABLE 3-continued

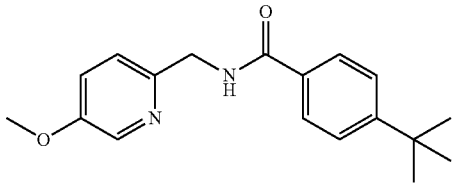
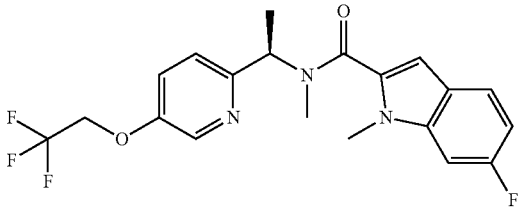
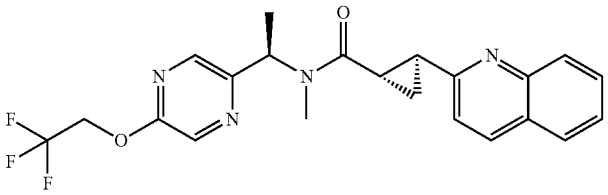
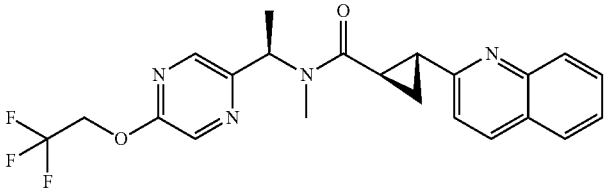
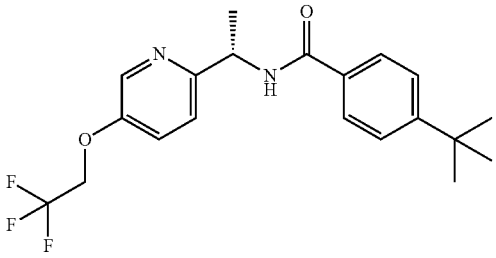
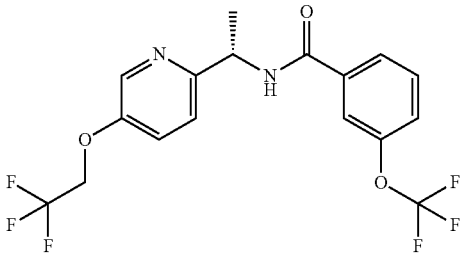
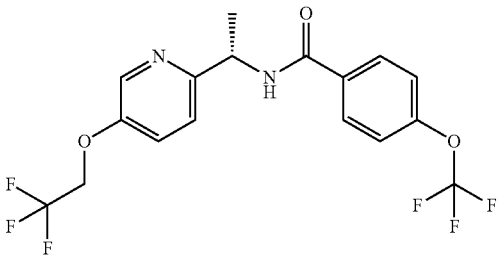
Example 423	4-(tert-butyl)-N-((5-methoxypyridin-2-yl)methyl)benzamide	
Example 424	(R)-6-fluoro-N,1-dimethyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 425	(1S*,2S*)-N-methyl-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 426	(1R*,2R*)-N-methyl-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide	
Example 427	(S)-4-(tert-butyl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 428	(S)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-3-(trifluoromethoxy)benzamide	
Example 429	(S)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-4-(trifluoromethoxy)benzamide	

TABLE 3-continued

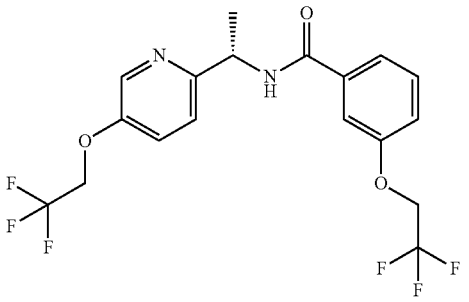
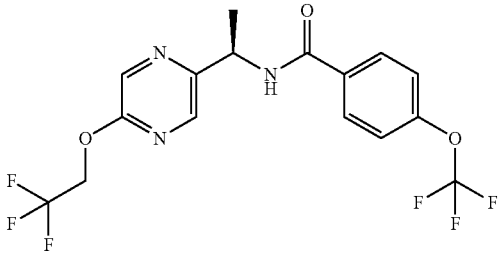
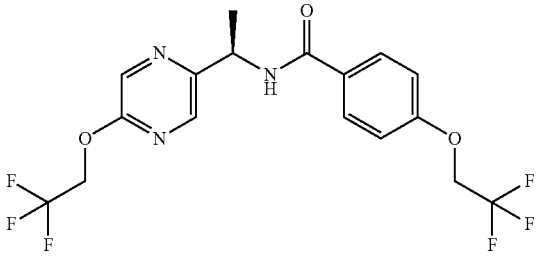
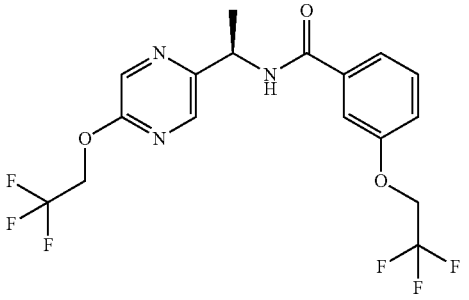
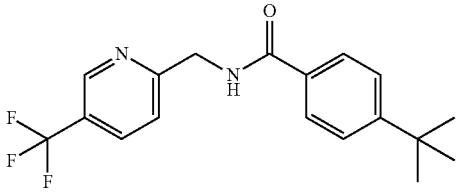
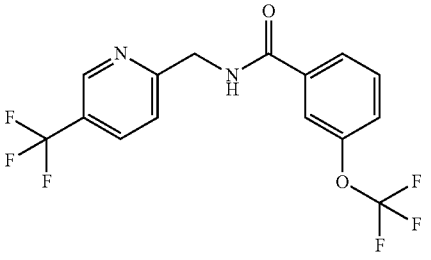
Example 430	(5)-3-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 431	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-4-(trifluoromethoxy)benzamide	
Example 432	(R)-4-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)benzamide	
Example 433	(R)-3-(2,2,2-N-(1-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)benzamide	
Example 434	4-(tert-butyl)-N-((5-(trifluoromethyl) pyridin-2-yl)methyl)benzamide	
Example 435	3-(trifluoromethoxy)-N-((5-(trifluoromethyl) pyridin-2-yl)methyl)benzamide	

TABLE 3-continued

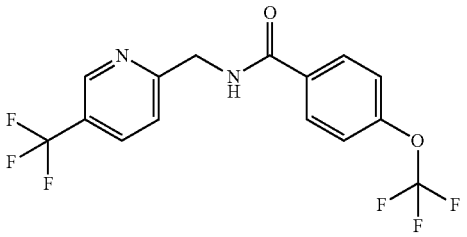
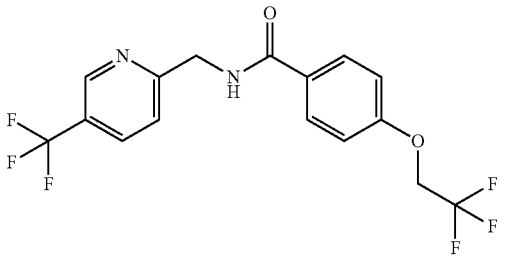
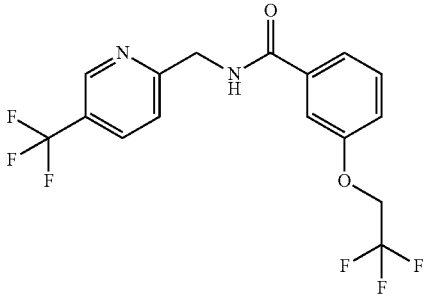
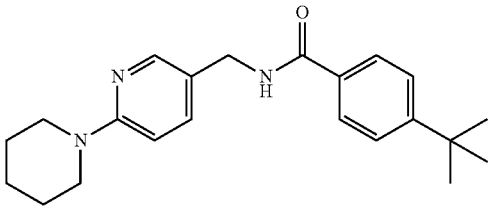
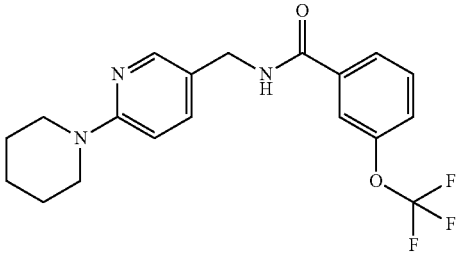
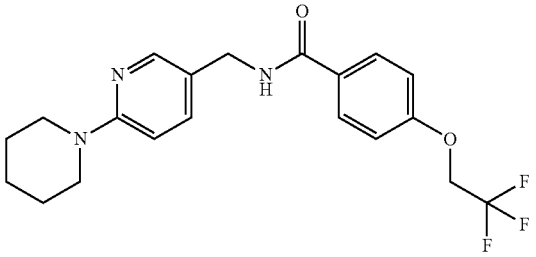
Example 436	4-(trifluoromethoxy)-N-((5-(trifluoromethyl) pyridin-2-yl)methyl)benzamide	
Example 437	4-(2,2,2-trifluoroethoxy)-N-((5-(trifluoromethyl) pyridin-2-yl)methyl)benzamide	
Example 438	3-(2,2,2-trifluoroethoxy)-N-((5-(trifluoromethyl) pyridin-2-yl)methyl)benzamide	
Example 439	4-(tert-butyl)-N-((6-(piperidin-1-yl)pyridin-3-yl)methyl)benzamide	
Example 440	N-((6-(piperidin-1-yl)pyridin-3-yl)methyl)-3-(trifluoromethoxy)benzamide	
Example 441	N-((6-(piperidin-1-yl)pyridin-3-yl)methyl)-4-(2,2,2-trifluoroethoxy)benzamide	

TABLE 3-continued

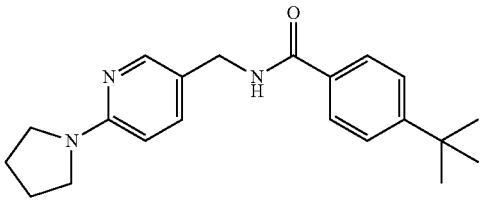
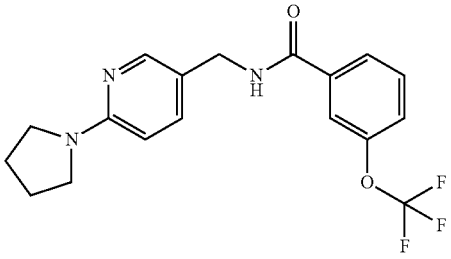
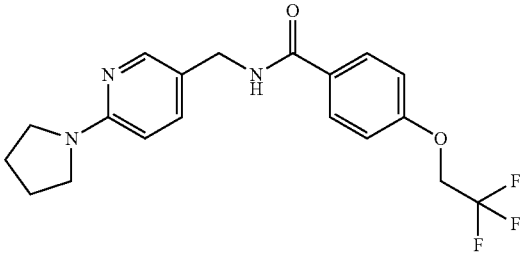
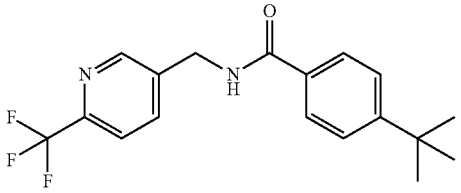
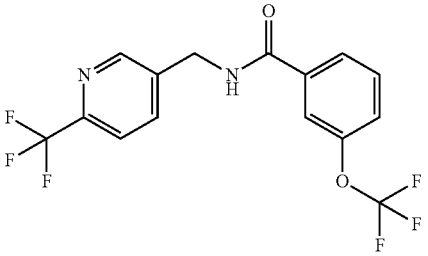
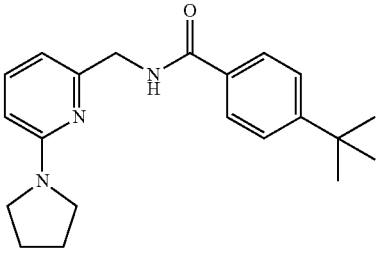
Example 442	4-(tert-butyl)-N-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)benzamide	
Example 443	N-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-3-(trifluoromethoxy)benzamide	
Example 444	N-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-4-(2,2,2-trifluoroethoxy)benzamide	
Example 445	4-(tert-butyl)-N-((6-(trifluoromethyl) pyridin-3-yl)methyl)benzamide	
Example 446	3-(trifluoromethoxy)-N-((6-(trifluoromethyl) pyridin-3-yl)methyl)benzamide	
Example 447	4-(tert-butyl)-N-((6-(pyrrolidin-1-yl)pyridin-2-yl)methyl)benzamide	

TABLE 3-continued

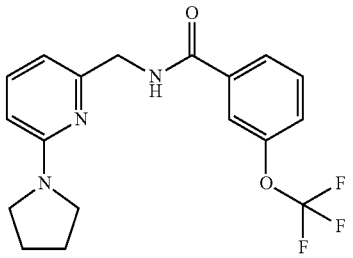
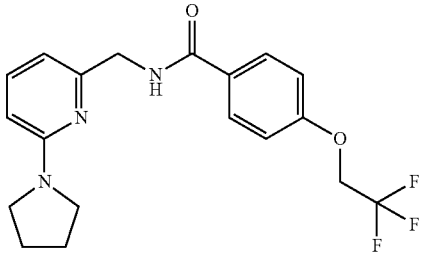
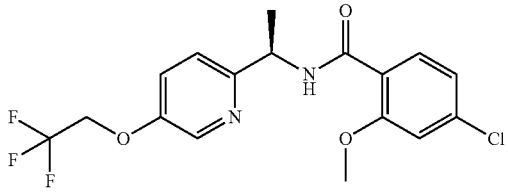
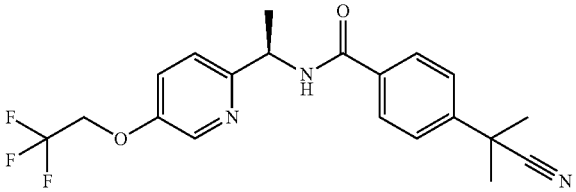
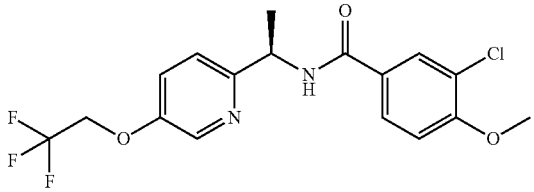
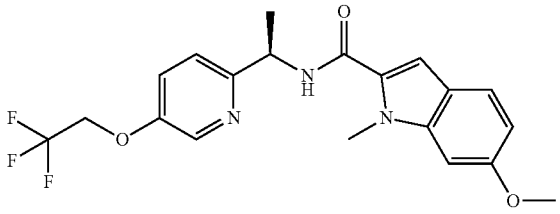
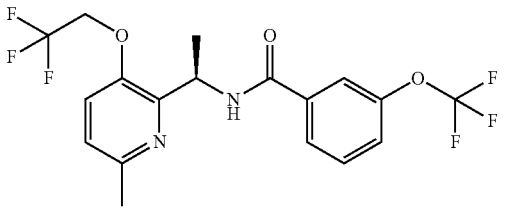
Example 448	N-((6-(pyrrolidin-1-yl)pyridin-2-yl) methyl)-3-(trifluoromethoxy)benzamide	
Example 449	N-((6-(pyrrolidin-1-yl)pyridin-2-yl)methyl)-4-(2,2,2-trifluoroethoxy)benzamide	
Example 450	(R)-4-chloro-2-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 451	(N)-4-(2-cyanopropan-2-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 452	(R)-3-chloro-4-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 453	(R)-6-methoxy-1-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-1H-indole-2-carboxamide	
Example 454	(R)-N-(1-(6-methyl-3-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)-3-(trifluoromethoxy)benzamide	

TABLE 3-continued

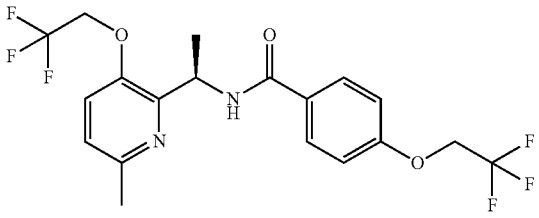
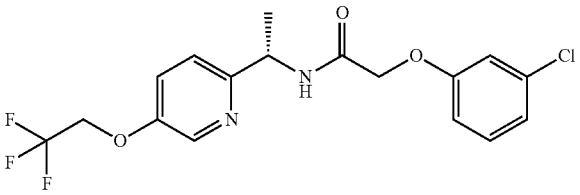
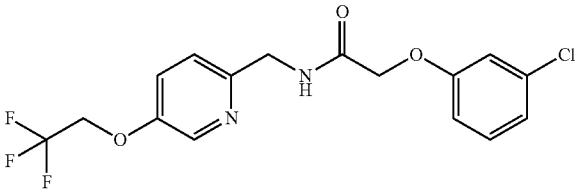
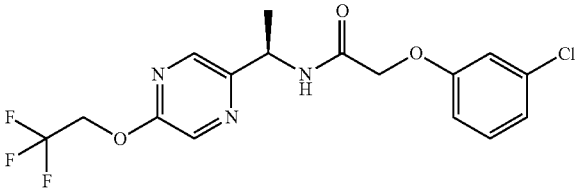
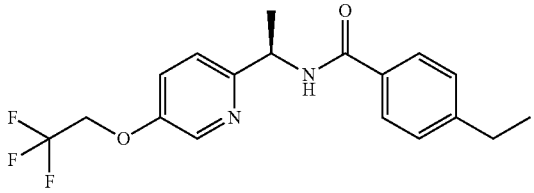
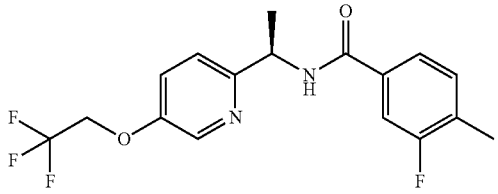
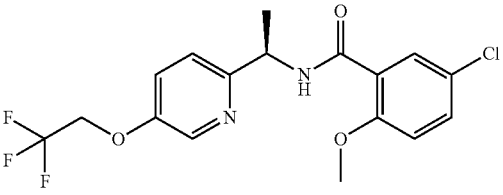
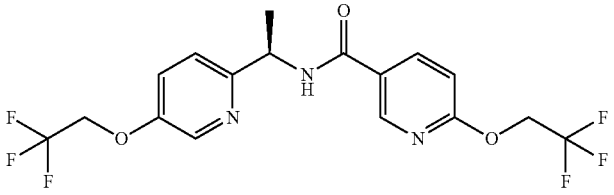
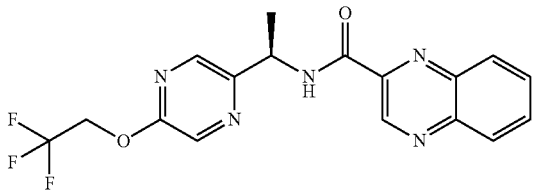
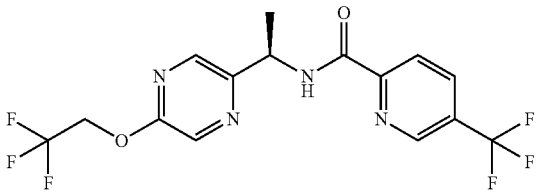
Example 455	(R)-N-(1-(6-methyl-3-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)-4-(2,2,2-trifluoroethoxy)benzamide	
Example 456	(S)-2-(3-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acetamide	
Example 457	2-(3-chlorophenoxy)-N-((5-(2,2,2-trifluoroethoxy) pyridin-2-yl)methyl)acetamide	
Example 458	(R)-2-(3-chlorophenoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)acetamide	
Example 459	(R)-4-ethyl-N-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl)benzamide	
Example 460	(R)-3-fluoro-4-methyl-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 461	(R)-5-chloro-2-methoxy-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)benzamide	
Example 462	(R)-6-(2,2,2-trifluoroethoxy)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)nicotinamide	

TABLE 3-continued

Example 463	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)quinoxaline-2-carboxamide	
Example 464	(R)-N-(1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-5-(trifluoromethyl)picolinamide	

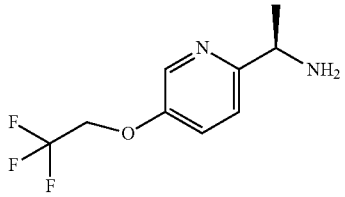
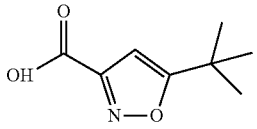
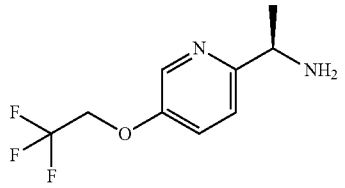
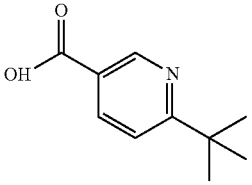
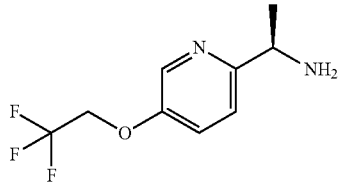
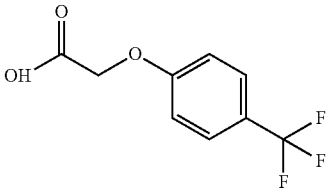
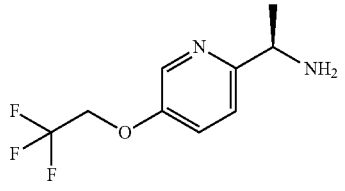
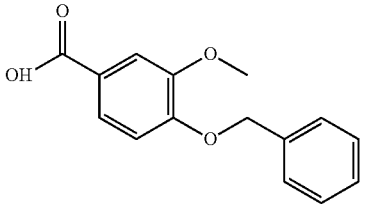
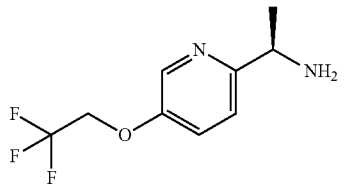
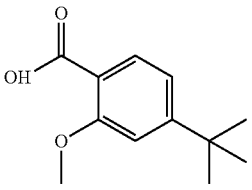
Example	Structure of amine part	Structure of caboxylic acid part	Observed MS	Retention Time	Purification Method
Example 1			372.0	0.85 min	HPLC
Example 2			382.0	0.79 min	HPLC
Example 3			423.0	0.83 min	HPLC
Example 4			461.0	0.82 min	HPLC
Example 5			411.0	0.9 min	HPLC

TABLE 3-continued

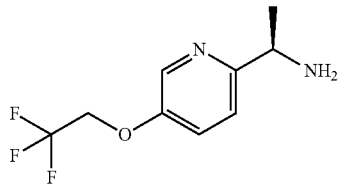
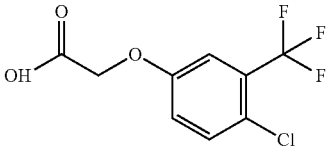
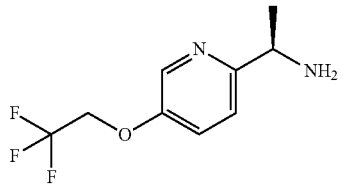
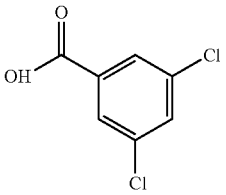
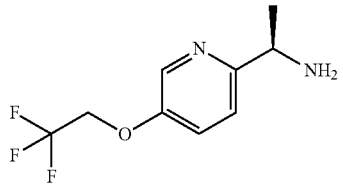
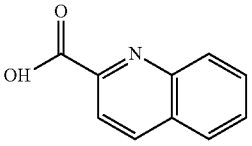
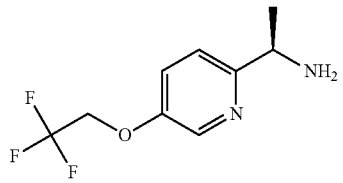
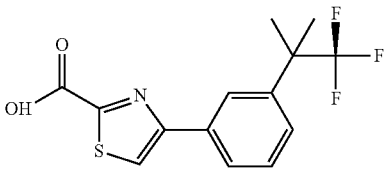
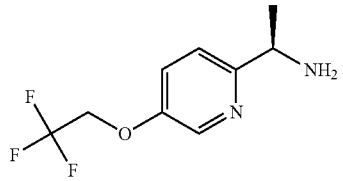
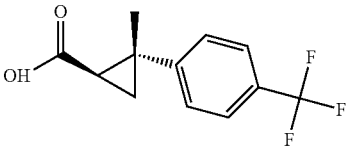
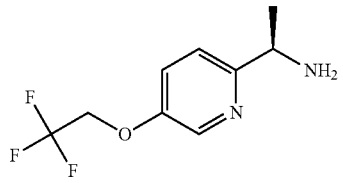
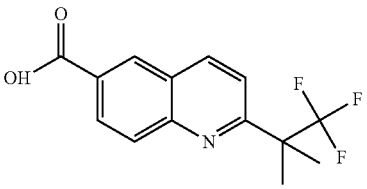
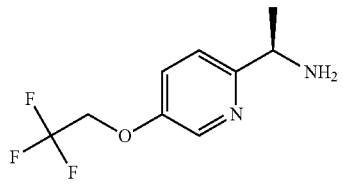
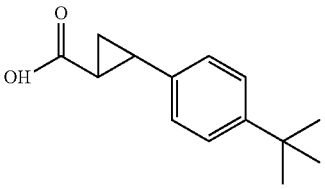
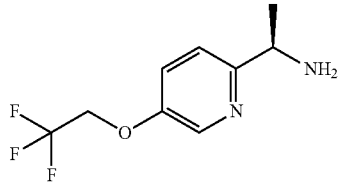
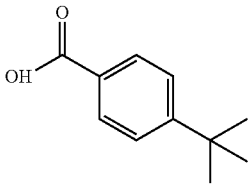
Example 6			457.0	0.86 min	HPLC
Example 7			393.0	0.86 min	HPLC
Example 8			376.0	0.83 min	HPLC
Example 9			518.0	2.08 min	HPLC
Example 10			447.0	1.91 min	HPLC
Example 11			486.0	1.94 min	HPLC
Example 12			421.0	1.99 min	HPLC
Example 13			381.2	1.89 min	HPLC

TABLE 3-continued

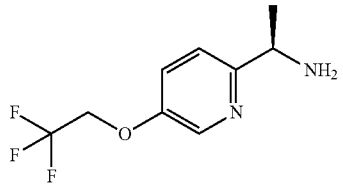
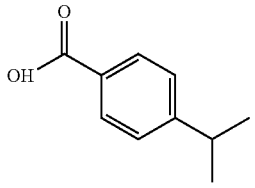
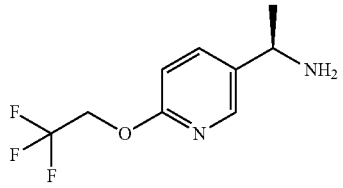
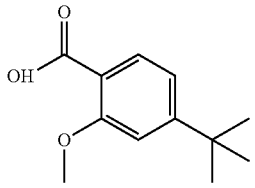
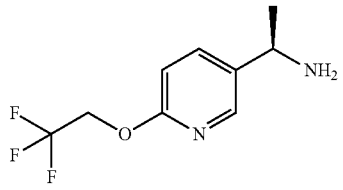
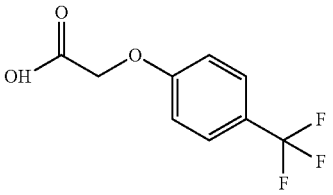
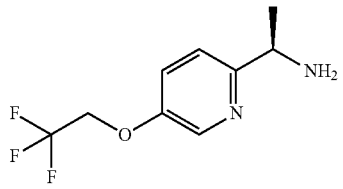
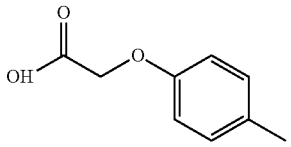
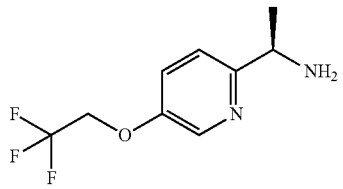
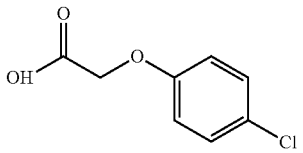
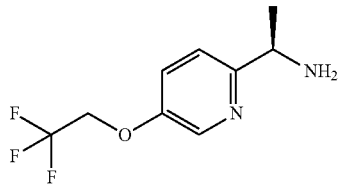
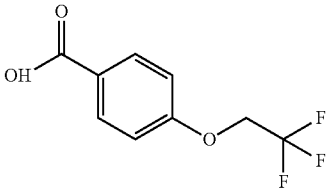
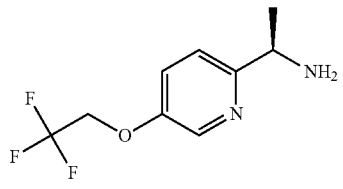
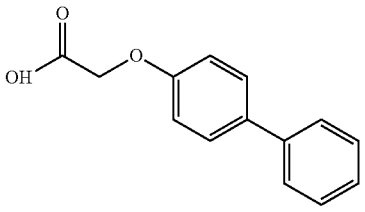
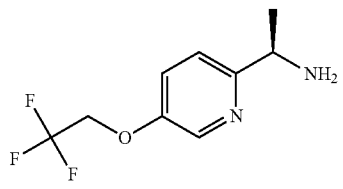
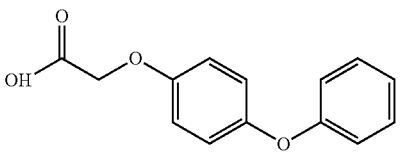
Example 14			367.2	1.83 min	HPLC
Example 15			411.2	2.06 min	HPLC
Example 16			423.1	3.24 min	HPLC
Example 17			369.1	1.77 min	HPLC
Example 18			389.1	1.78 min	HPLC
Example 19			423.1	1.73 min	HPLC
Example 20			431.1	1.90 min	HPLC
Example 21			447.1	1.89 min	HPLC

TABLE 3-continued

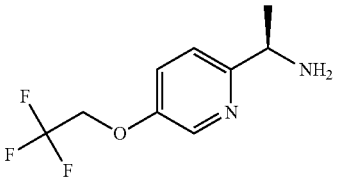
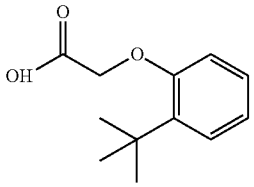
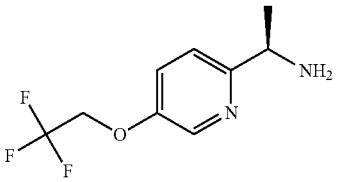
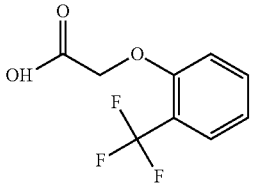
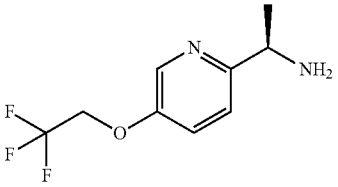
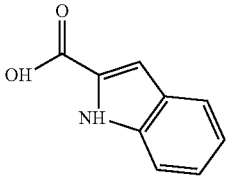
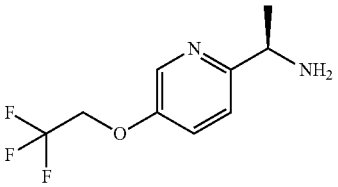
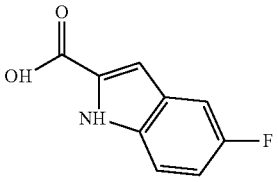
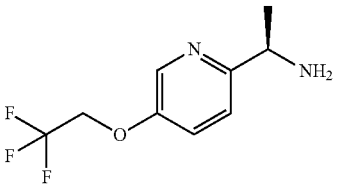
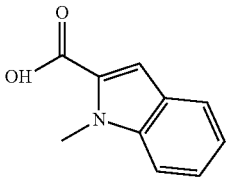
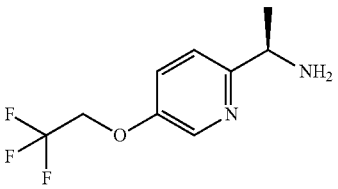
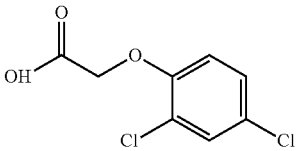
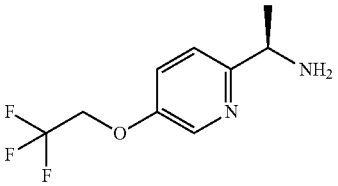
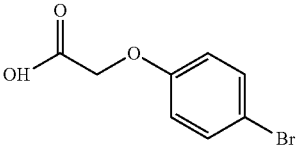
Example 22			411.2	2.04 min	HPLC
Example 23			423.1	1.84 min	HPLC
Example 24			364.2	1.67 min	HPLC
Example 25			382.2	1.69 min	HPLC
Example 26			378.2	1.80 min	HPLC
Example 27			423.1	1.92 min	HPLC
Example 28			433.1	1.80 min	HPLC
Example 29	Alternative route		395.2	1.84 min	HPLC

TABLE 3-continued

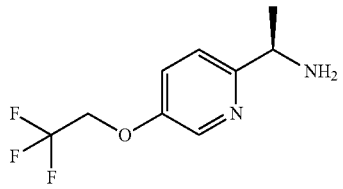
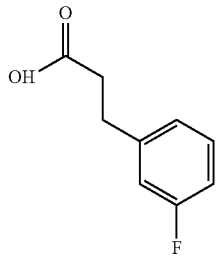
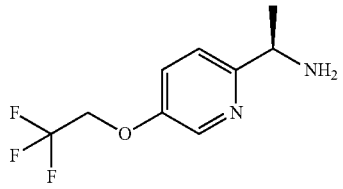
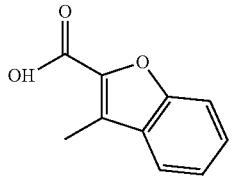
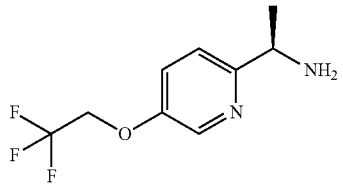
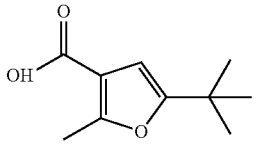
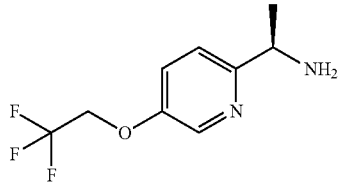
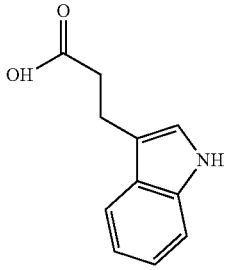
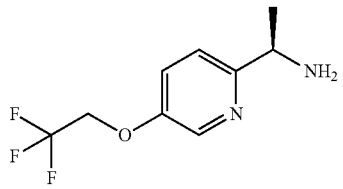
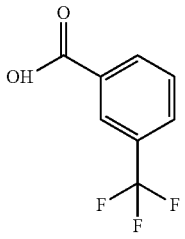
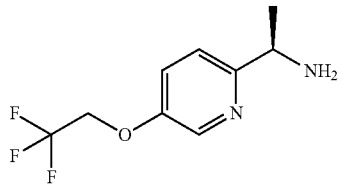
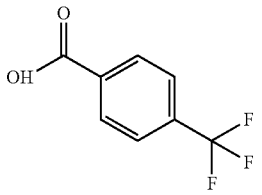
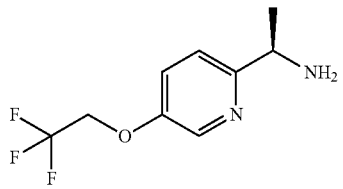
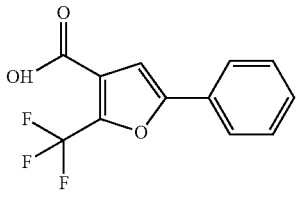
Example 30			371.2	1.65 min	HPLC
Example 31			379.2	1.88 min	HPLC
Example 32			385.2	1.93 min	HPLC
Example 33			392.2	1.59 min	HPLC
Example 34			393.2	1.76 min	HPLC
Example 35			393.2	1.76 min	HPLC
Example 36			459.2	1.96 min	HPLC

TABLE 3-continued

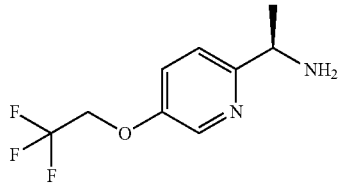
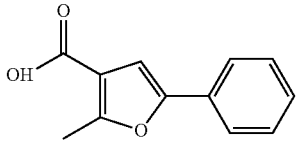
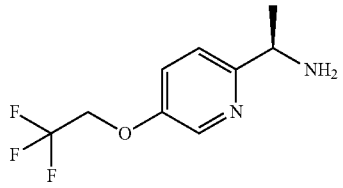
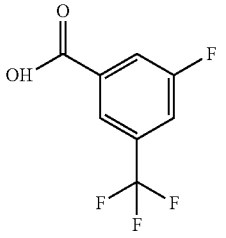
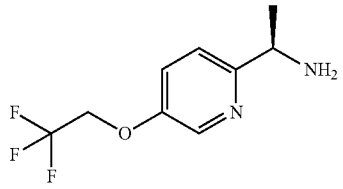
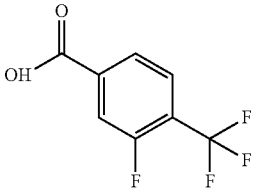
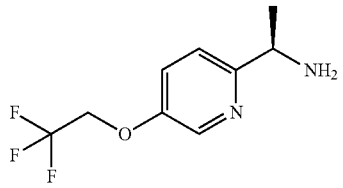
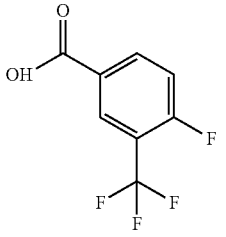
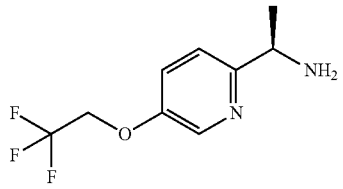
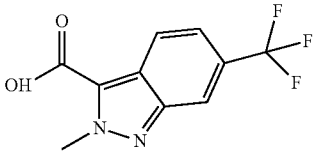
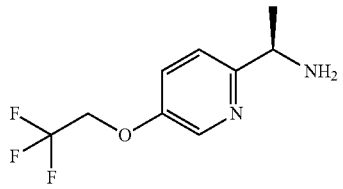
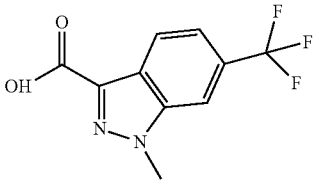
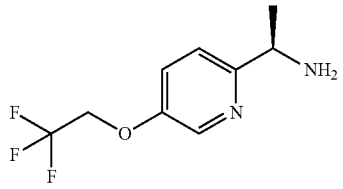
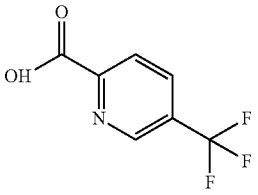
Example 37			405.2	1.89 min	HPLC
Example 38			411.2	1.83 min	HPLC
Example 39			411.2	1.81 min	HPLC
Example 40			411.2	1.79 min	HPLC
Example 41			446.9	1.87 min	HPLC
Example 42			446.9	1.89 min	HPLC
Example 43			393.9	1.83 min	HPLC

TABLE 3-continued

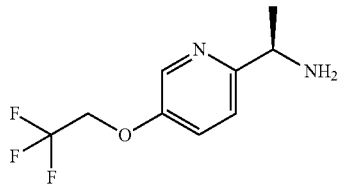
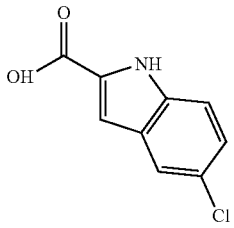
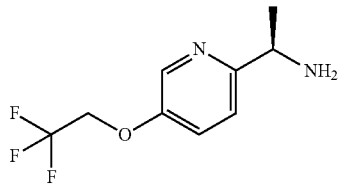
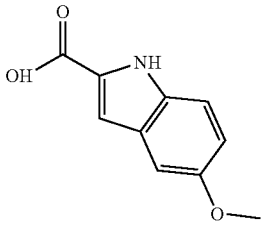
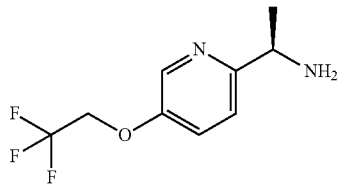
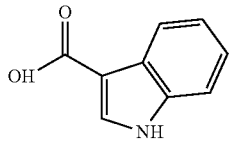
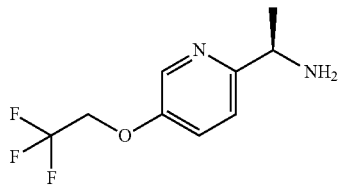
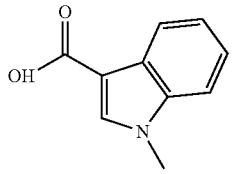
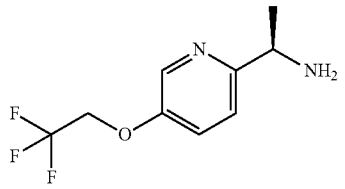
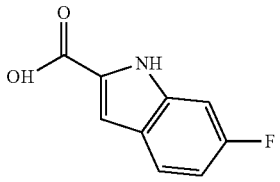
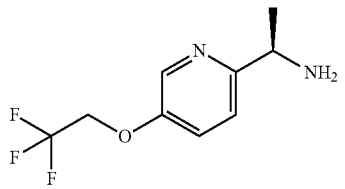
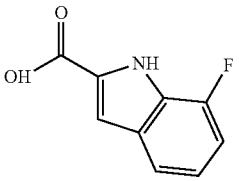
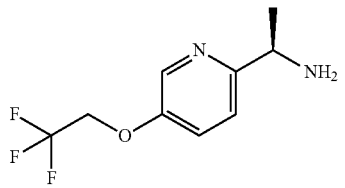
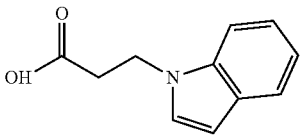
Example 44			398.0	1.77 min	HPLC
Example 45			394.0	1.64 min	HPLC
Example 46			364.0	1.55 min	HPLC
Example 47			378.0	1.66 min	HPLC
Example 48			382.0	1.70 min	HPLC
Example 49			382.0	1.70 min	HPLC
Example 50			392.0	1.70 min	HPLC

TABLE 3-continued

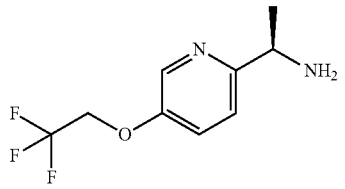
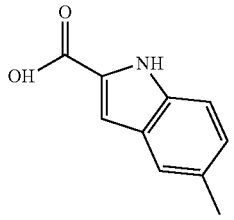
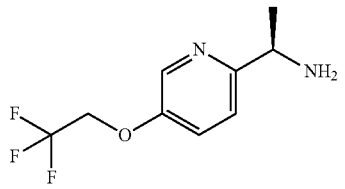
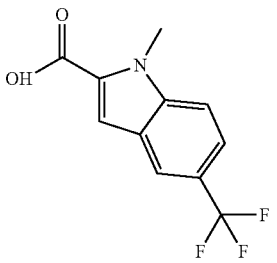
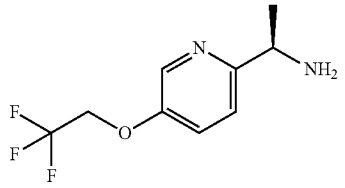
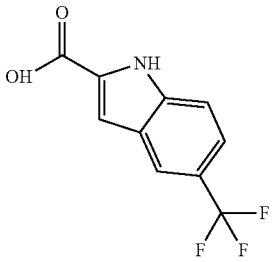
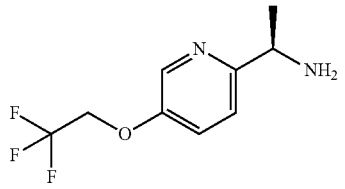
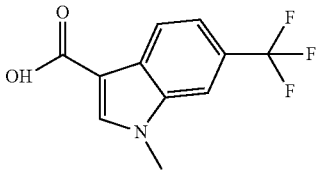
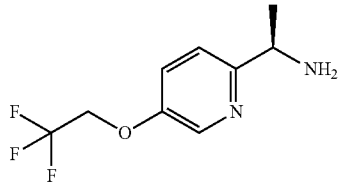
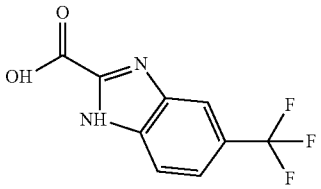
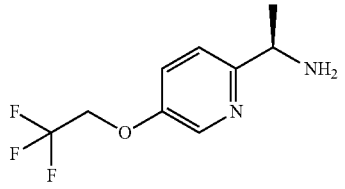
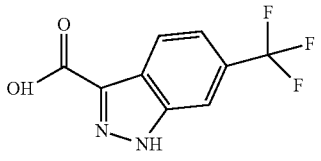
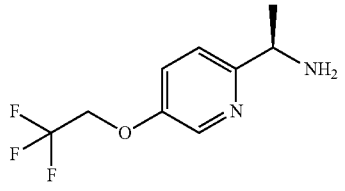
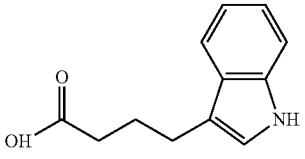
Example 51			378.0	1.76 min	HPLC
Example 52			446.0	1.93 min	HPLC
Example 53			432.0	1.82 min	HPLC
Example 54			446.0	1.81 min	HPLC
Example 55			432.9	1.80 min	HPLC
Example 56			432.9	1.76 min	HPLC
Example 57			406.0	1.65 min	HPLC

TABLE 3-continued

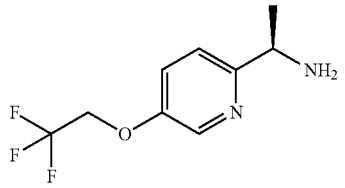
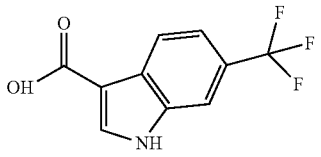
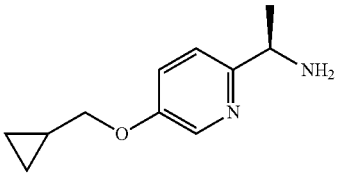
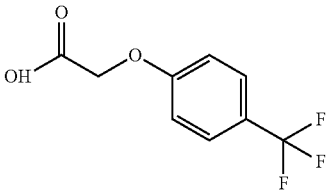
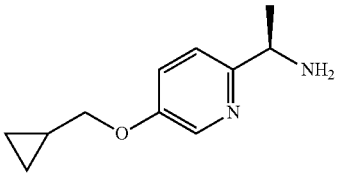
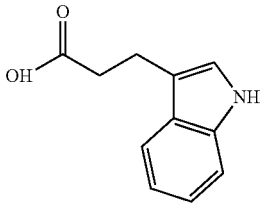
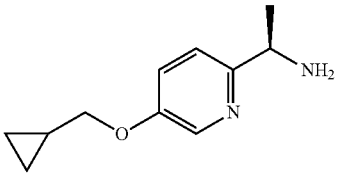
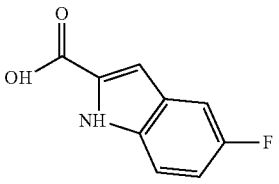
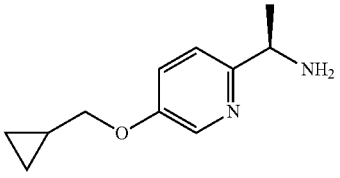
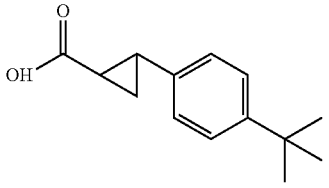
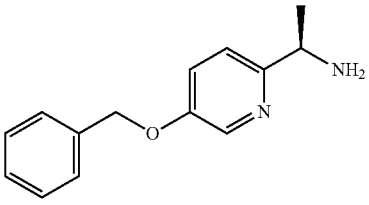
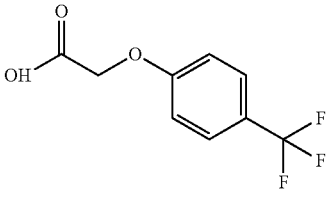
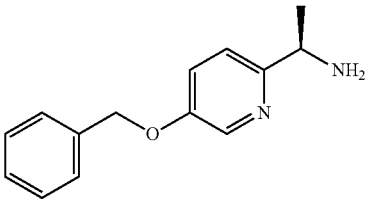
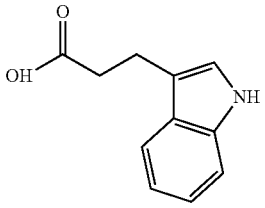
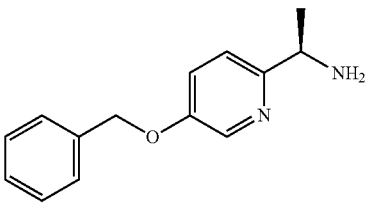
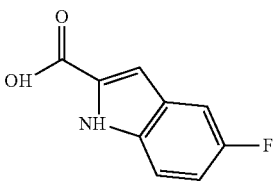
Example 58			431.9	1.73 min	HPLC
Example 59			395.0	1.87 min	HPLC
Example 60			364.0	1.62 min	HPLC
Example 61			354.0	1.74 min	HPLC
Example 62			393.0	2.06 min	HPLC
Example 63			430.9	1.94 min	HPLC
Example 64			400.0	1.72 min	HPLC
Example 65			390.0	1.82 min	HPLC

TABLE 3-continued

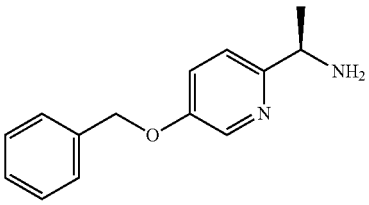
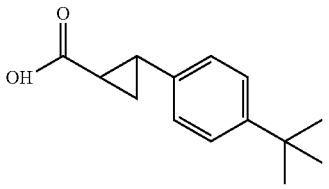
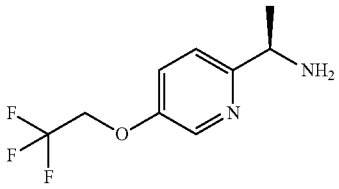
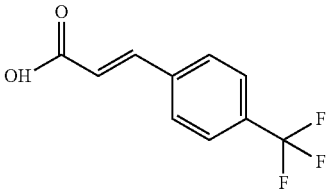
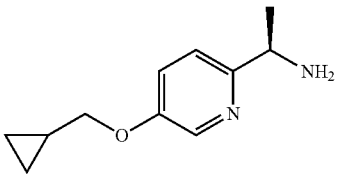
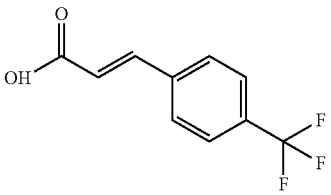
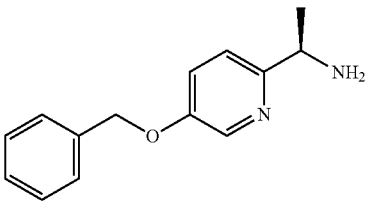
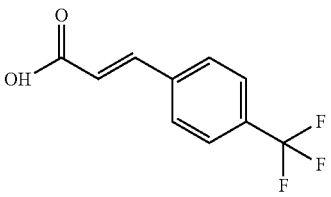
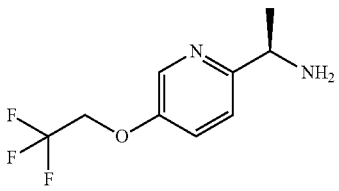
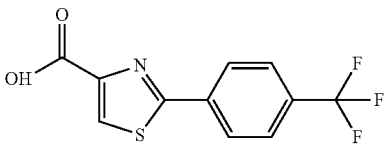
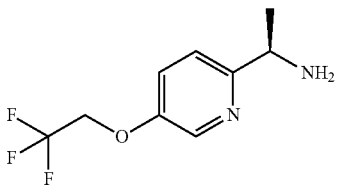
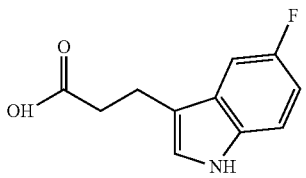
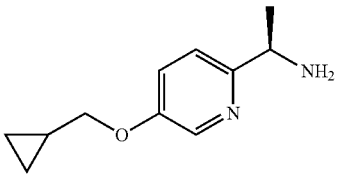
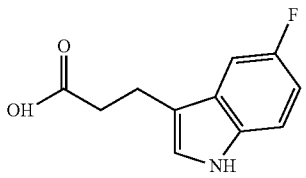
Example 66			429.0	2.11 min	HPLC
Example 67			418.9	1.82 min	HPLC
Example 68			391.0	1.85 min	HPLC
Example 69			427.0	1.92 min	HPLC
Example 70			475.9	2.01 min	HPLC
Example 71			410.0	1.62 min	HPLC
Example 72			382.0	1.64 min	HPLC

TABLE 3-continued

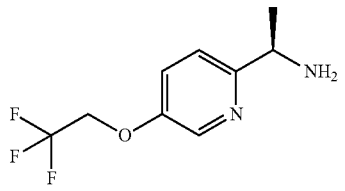
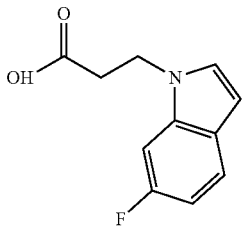
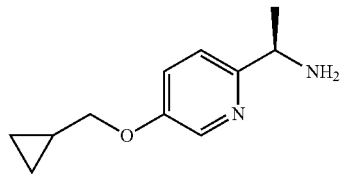
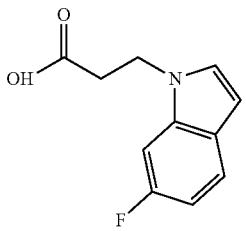
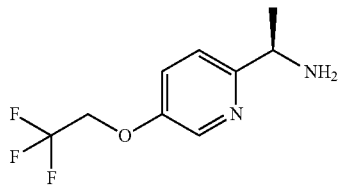
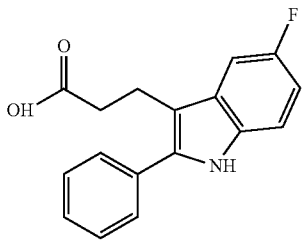
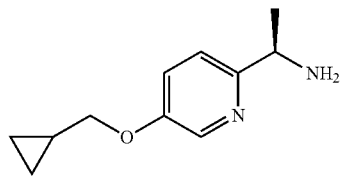
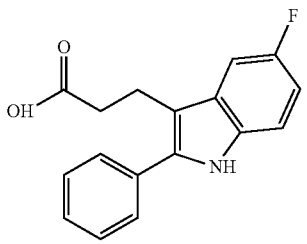
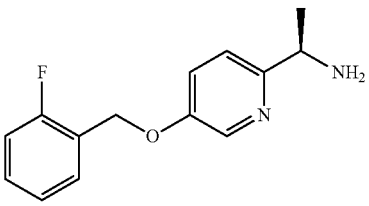
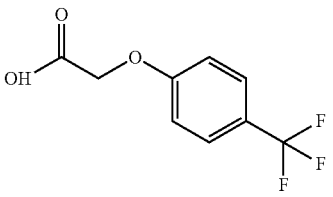
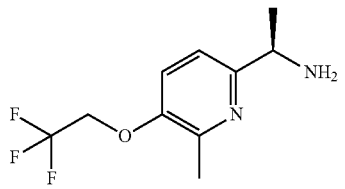
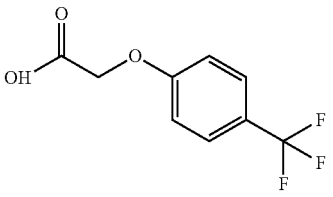
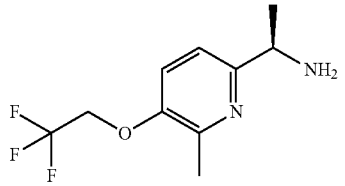
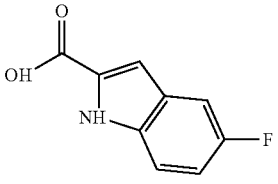
Example 73			410.0	1.73 min	HPLC
Example 74			382.0	1.76 min	HPLC
Example 75			486.0	1.81 min	HPLC
Example 76			458.1	1.84 min	HPLC
Example 77			449.1	3.24 min	HPLC
Example 78			436.9	1.92 min	HPLC
Example 79			395.9	1.80 min	HPLC

TABLE 3-continued

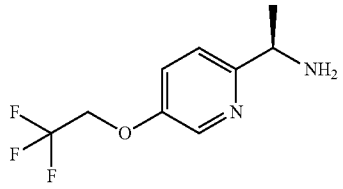
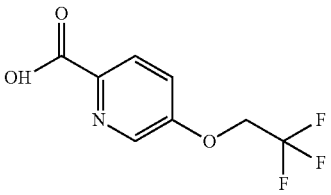
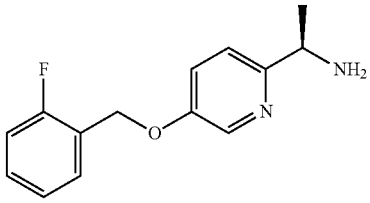
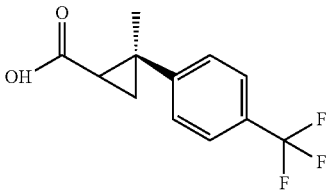
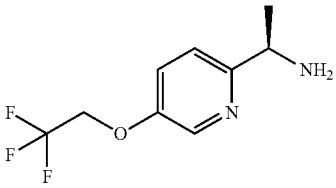
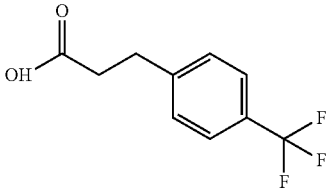
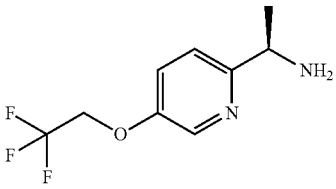
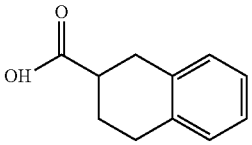
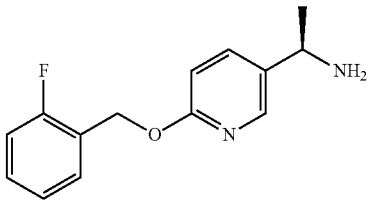
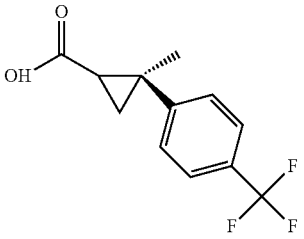
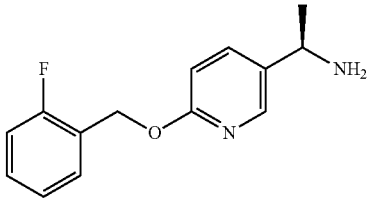
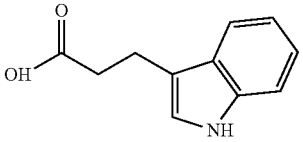
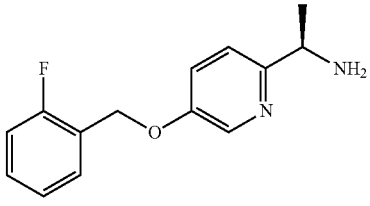
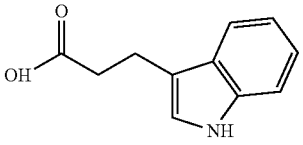
Example 80			423.9	1.79 min	HPLC
Example 81	Alternative route		431.9	1.68 min	HPLC
Example 82			472.9	2.04 min	HPLC
Example 83			420.9	1.77 min	HPLC
Example 84			378.9	1.77 min	HPLC
Example 85			473.0	2.09 min	HPLC
Example 86			418.0	1.79 min	HPLC
Example 87			418.0	1.72 min	HPLC

TABLE 3-continued

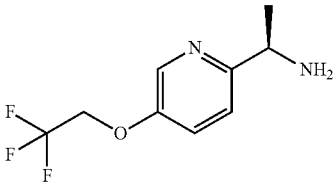
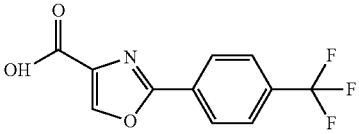
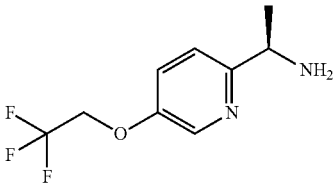
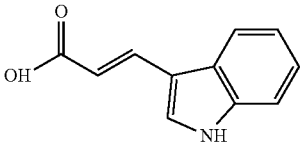
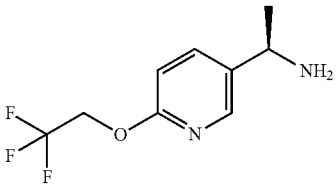
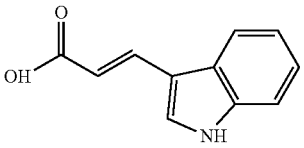
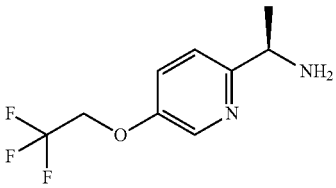
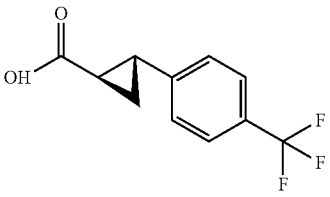
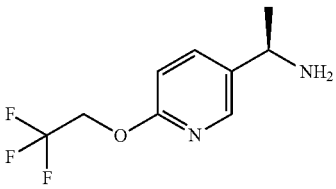
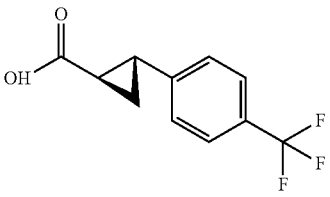
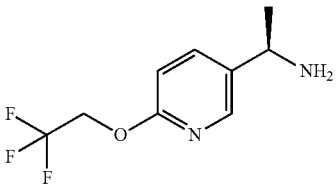
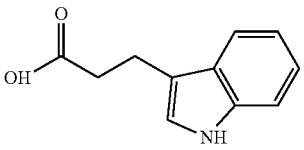
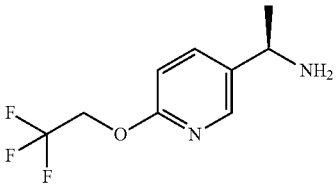
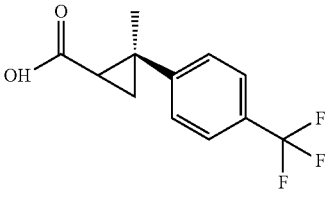
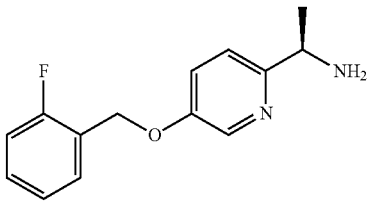
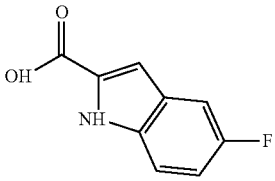
Example 88			459.9	1.95 min	HPLC
Example 89			389.9	1.60 min	HPLC
Example 90			389.9	1.71 min	HPLC
Example 91			433.1	3.15 min	HPLC
Example 92			433.1	3.32 min	HPLC
Example 93			392.2	2.92 min	HPLC
Example 94			447.1	3.47 min	HPLC
Example 95			408.2	3.04 min	HPLC

TABLE 3-continued

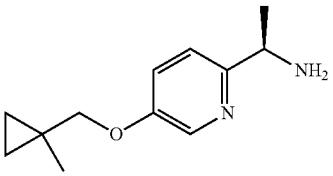
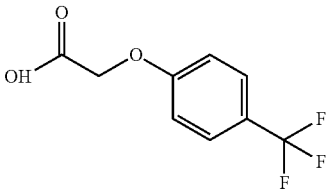
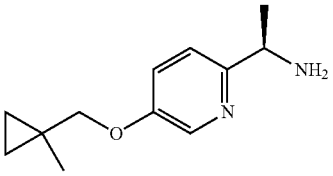
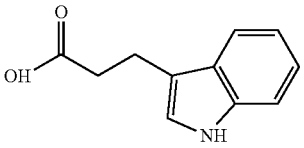
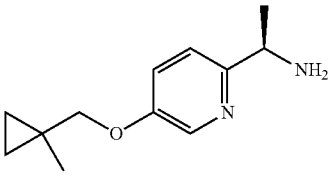
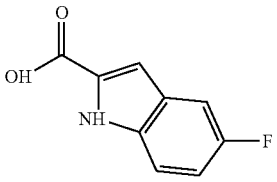
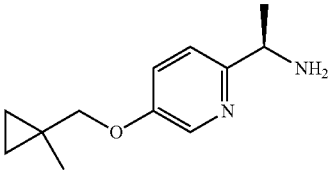
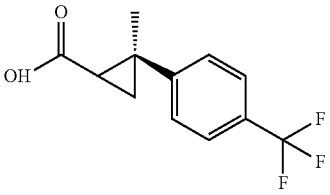
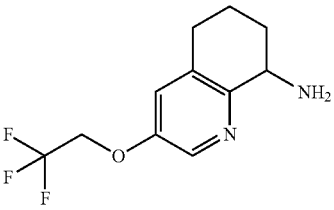
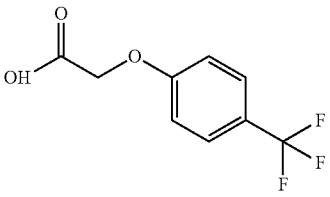
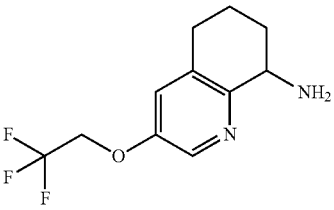
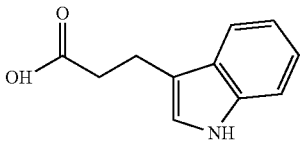
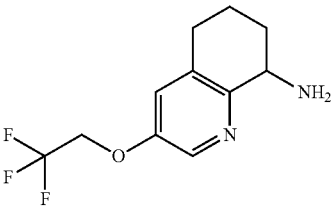
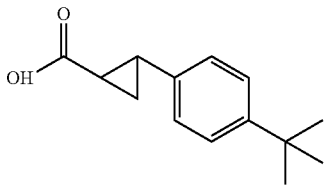
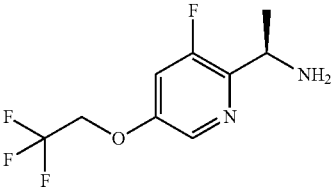
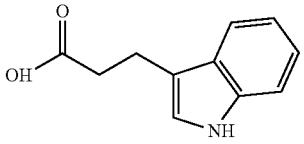
Example 96			409.2	3.34 min	HPLC
Example 97			378.2	2.80 min	HPLC
Example 98			368.2	3.09 min	HPLC
Example 99			433.2	3.49 min	HPLC
Example 100			449.2	3.19 min	HPLC
Example 101			418.2	2.77 min	HPLC
Example 102			447.2	3.47 min	HPLC
Example 103			409.9	1.68 min	HPLC

TABLE 3-continued

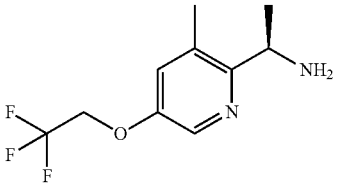
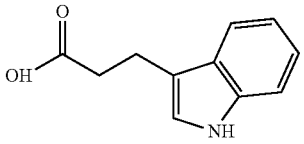
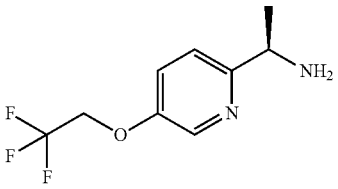
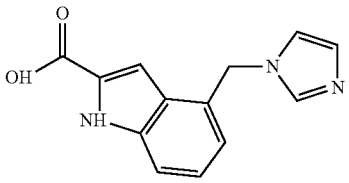
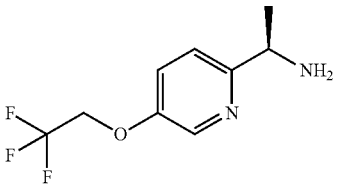
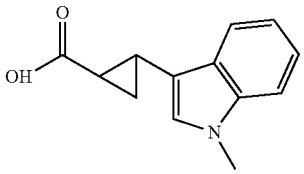
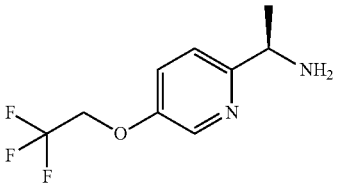
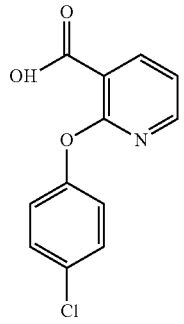
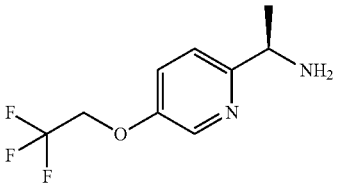
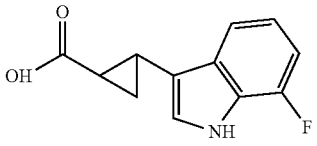
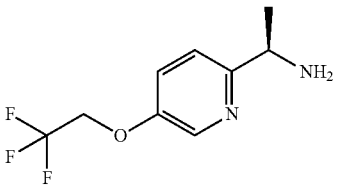
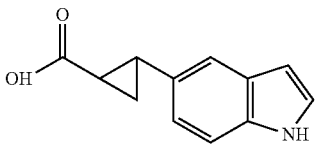
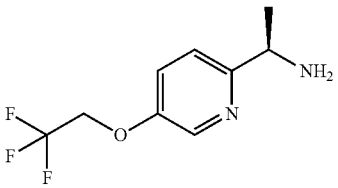
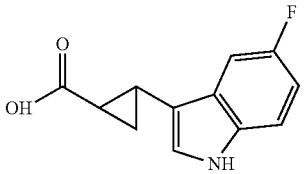
Example 104			406.0	1.70 min	HPLC
Example 105			444.1	1.47 min	HPLC
Example 105			417.9	1.77 min	HPLC
Example 107			451.9	1.92 min	HPLC
Example 108			421.9	1.68 min	HPLC
Example 109			403.9	1.61 min	HPLC
Example 110			421.9	1.65 min	HPLC

TABLE 3-continued

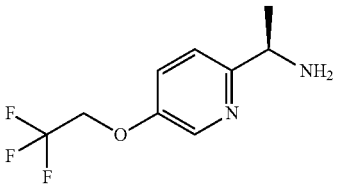
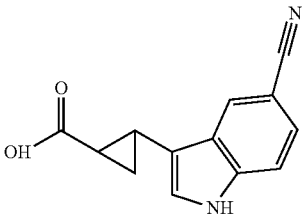
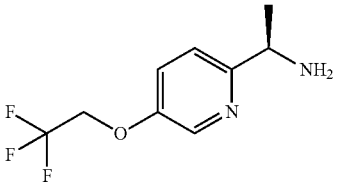
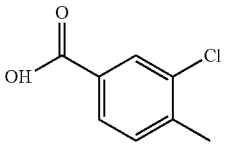
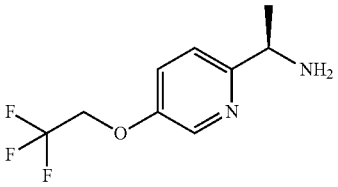
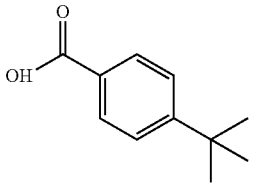
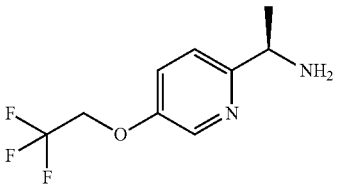
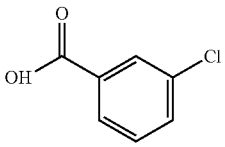
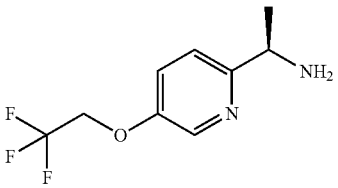
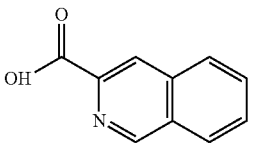
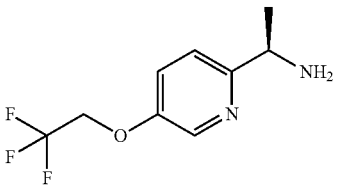
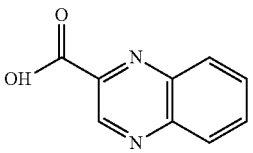
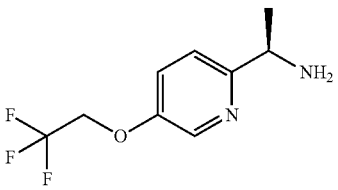
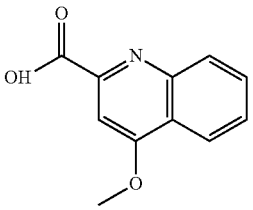
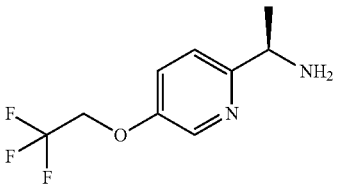
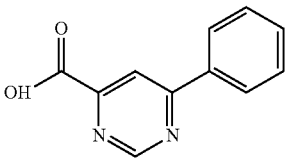
Example 111			429.0	1.57 min	HPLC
Example 112			372.9	1.80 min	HPLC
Example 113			381.0	1.98 min	HPLC
Example 114			358.9	1.72 min	HPLC
Example 115			375.9	1.77 min	HPLC
Example 116			376.9	1.70 min	HPLC
Example 117			405.9	1.90 min	HPLC
Example 118			402.9	1.87 min	HPLC

TABLE 3-continued

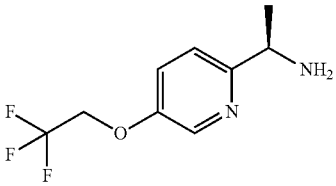
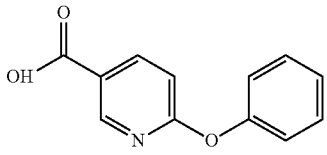
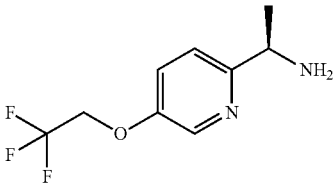
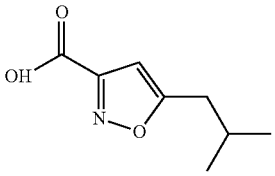
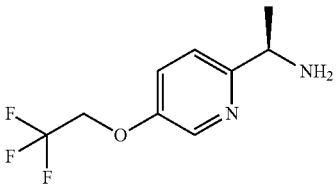
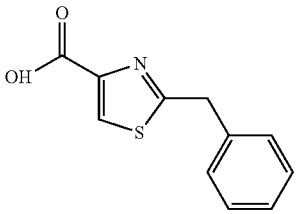
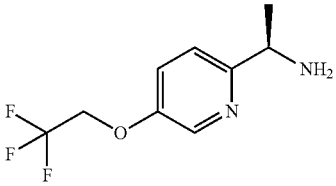
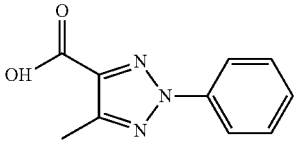
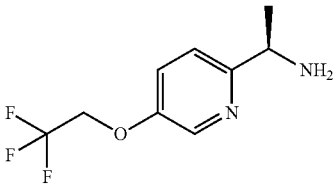
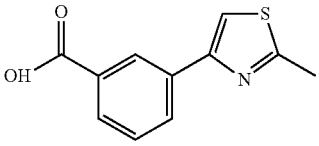
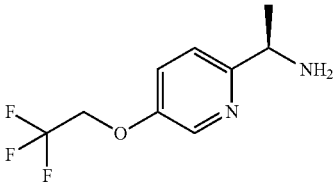
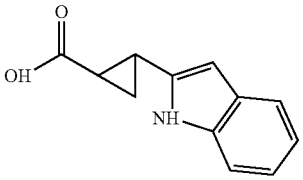
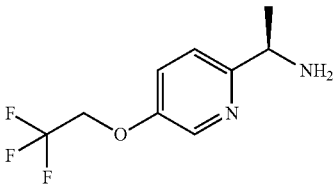
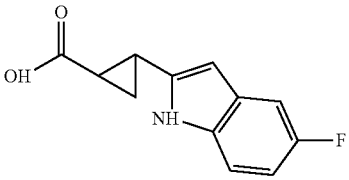
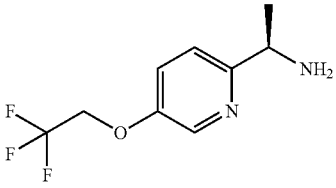
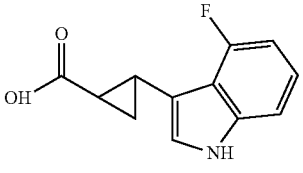
Example 119			417.9	1.72 min	HPLC
Example 120			371.9	1.86 min	HPLC
Example 121			421.9	1.85 min	HPLC
Example 122			405.9	1.92 min	HPLC
Example 123			421.9	1.70 min	HPLC
Example 124			404.0	1.72 min	HPLC
Example 125			422.0	1.72 min	HPLC
Example 126			422.0	1.64 min	HPLC

TABLE 3-continued

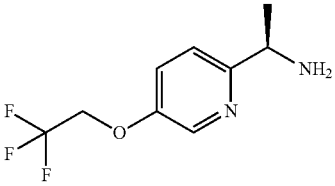
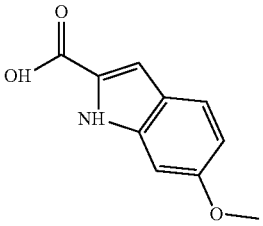
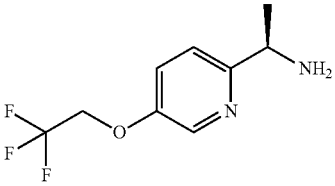
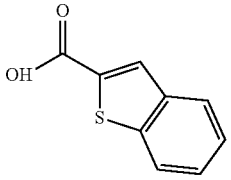
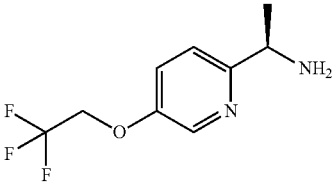
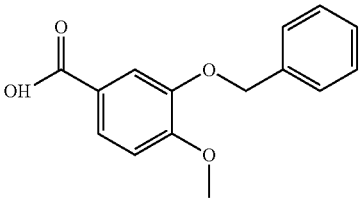
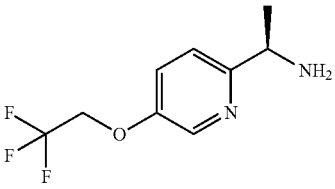
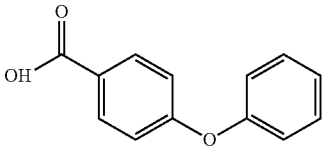
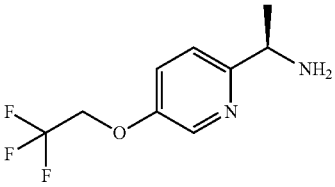
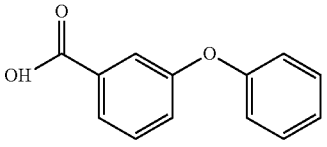
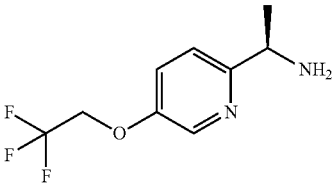
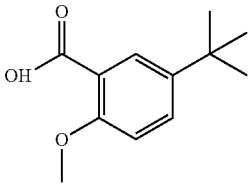
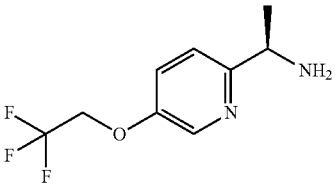
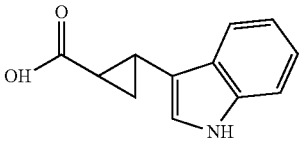
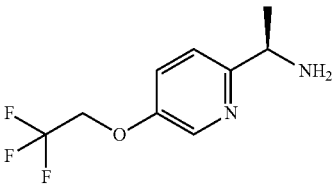
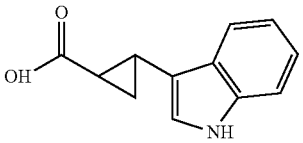
Example 127			394.0	1.66 min	HPLC
Example 128			380.9	1.78 min	HPLC
Example 129			460.9	1.80 min	HPLC
Example 130			416.9	1.86 min	HPLC
Example 131			416.9	1.88 min	HPLC
Example 132			411.0	1.99 min	HPLC
Example 133			Confirmed by NMR (see Table 2)		Chiral-HPLC
Example 134			Confirmed by NMR (see Table 2)		Chiral-HPLC

TABLE 3-continued

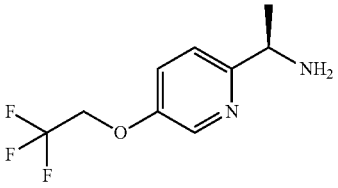
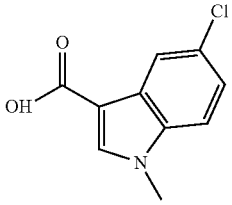
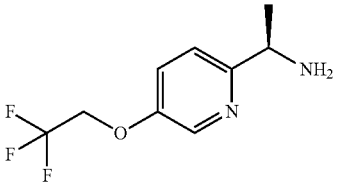
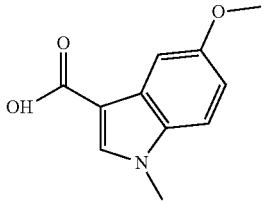
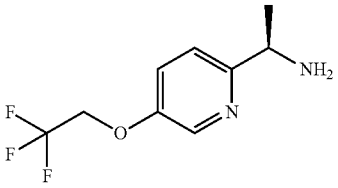
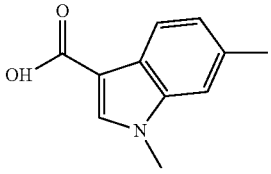
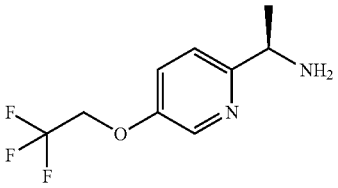
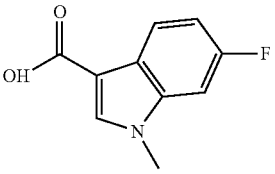
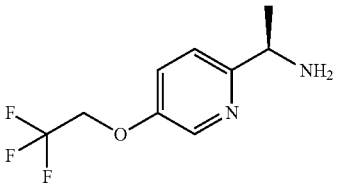
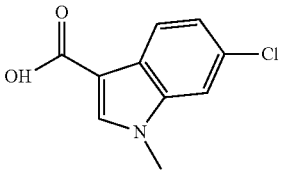
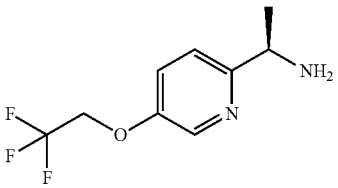
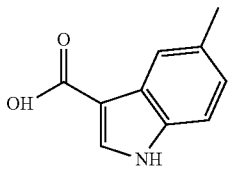
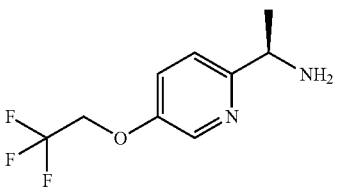
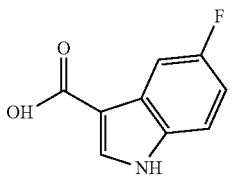
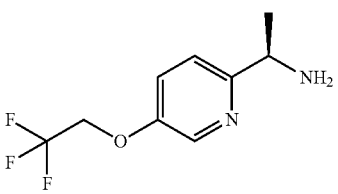
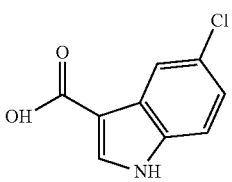
Example 135			410.1	1.75 min	HPLC
Example 136			406.2	1.63 min	HPLC
Example 137			390.1	1.74 min	HPLC
Example 138			394.1	1.68 min	HPLC
Example 139			410.1	1.77 min	HPLC
Example 140			376.2	1.62 min	HPLC
Example 141			380.2	1.57 min	HPLC
Example 142			396.1	1.65 min	HPLC

TABLE 3-continued

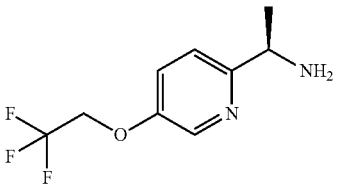
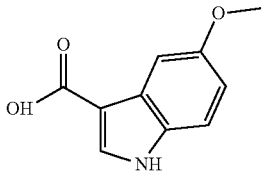
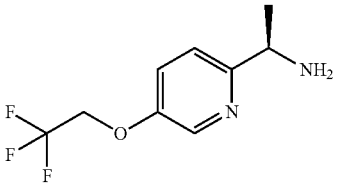
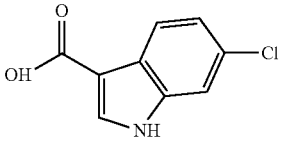
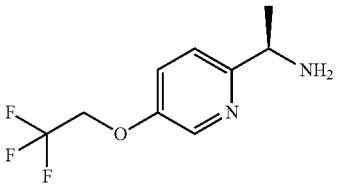
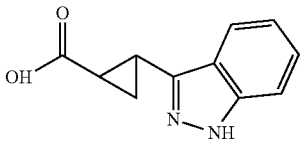
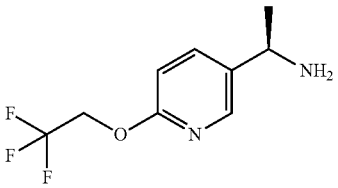
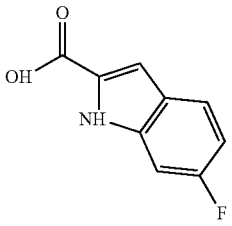
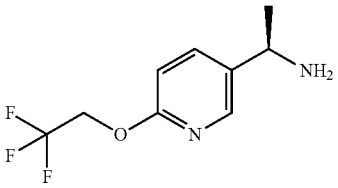
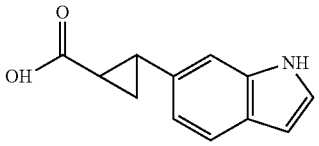
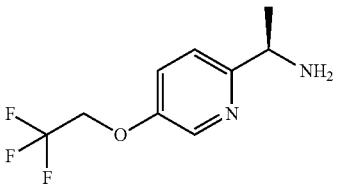
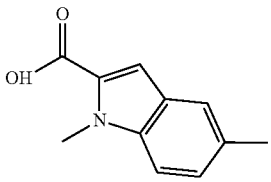
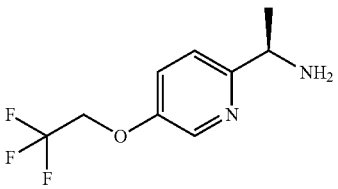
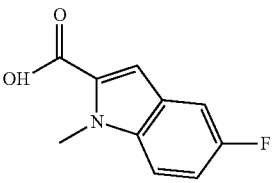
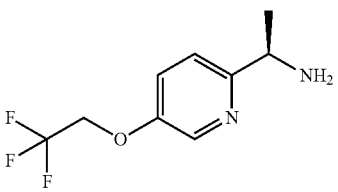
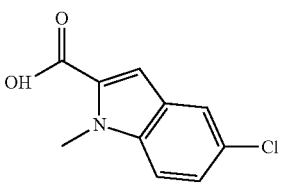
Example 143			392.1	1.53 min	HPLC
Example 144			396.1	1.65 min	HPLC
Example 145			403.2	1.52 min	HPLC
Example 146			380.2	1.78 min	HPLC
Example 147			402.2	1.75 min	HPLC
Example 148			390.2	1.85 min	HPLC
Example 149			394.2	1.80 min	HPLC
Example 150			410.1	1.90 min	HPLC

TABLE 3-continued

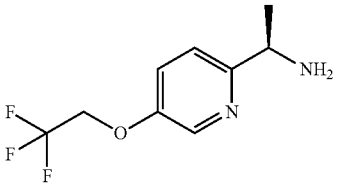
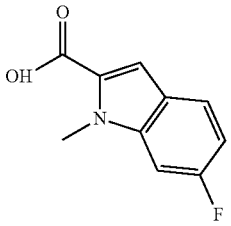
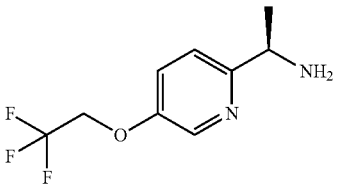
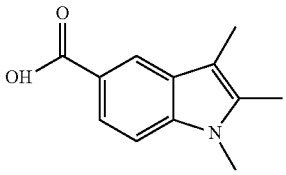
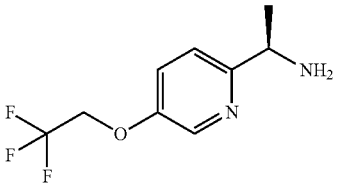
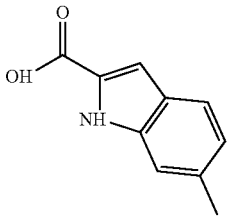
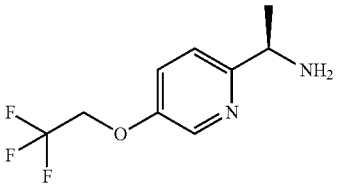
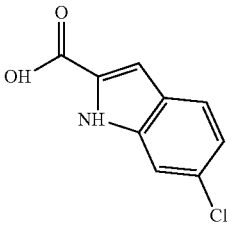
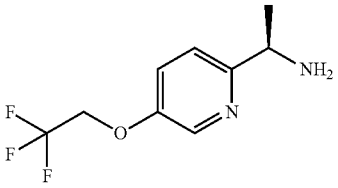
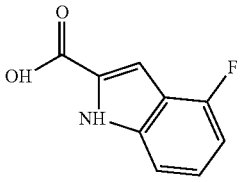
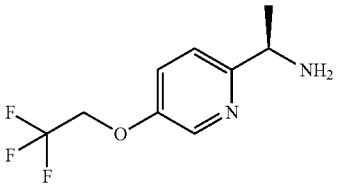
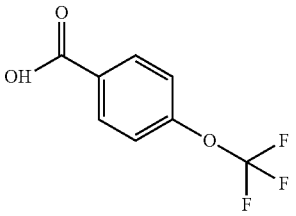
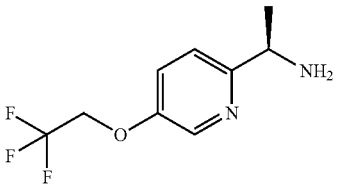
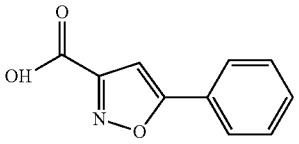
Example 151			394.1	1.81 min	HPLC
Example 152			404.1	1.77 min	HPLC
Example 153			376.0	1.73 min	HPLC
Example 154			395.9	1.78 min	HPLC
Example 155			380.0	1.71 min	HPLC
Example 156			406.9	1.81 min	HPLC
Example 157			390.0	1.84 min	HPLC

TABLE 3-continued

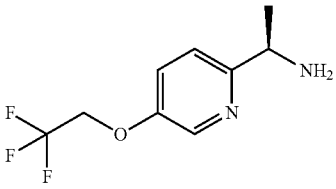
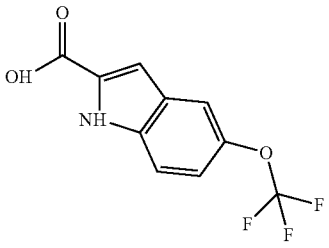
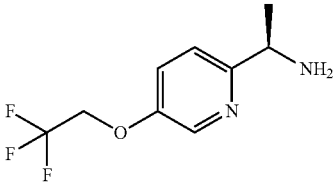
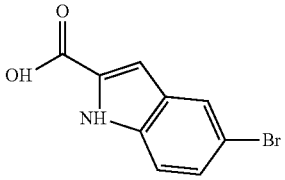
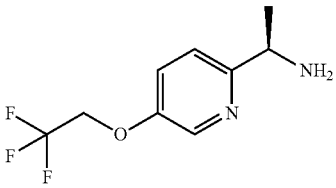
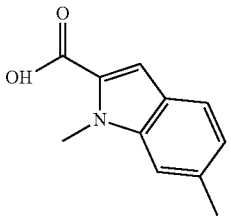
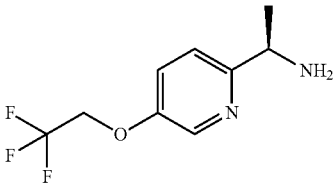
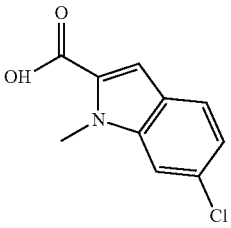
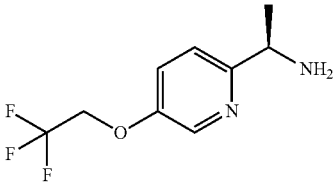
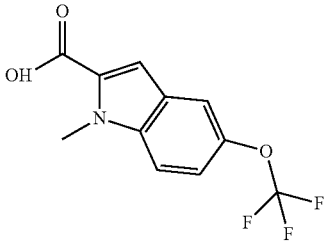
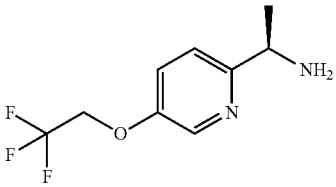
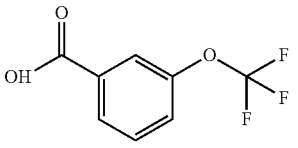
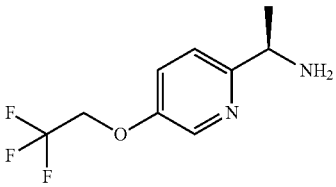
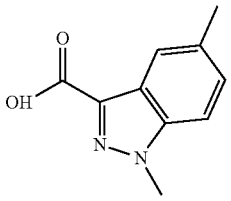
Example 158			445.9	1.83 min	HPLC
Example 159			439.8	1.80 min	HPLC
Example 160			390.0	1.87 min	HPLC
Example 161			410.0	1.90 min	HPLC
Example 162			459.9	1.94 min	HPLC
Example 163			406.9	1.79 min	HPLC
Example 164			393.0	1.81 min	HPLC

TABLE 3-continued

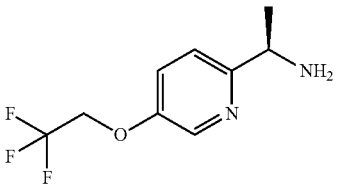
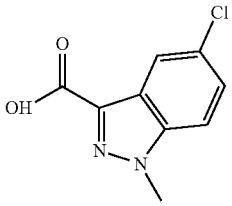
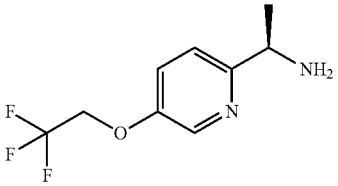
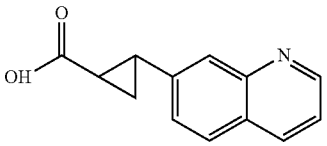
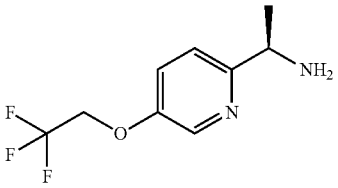
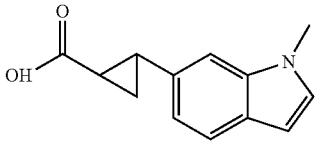
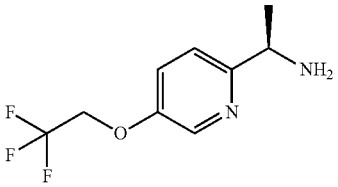
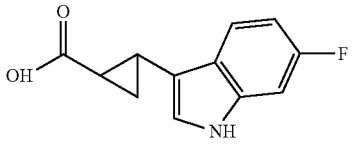
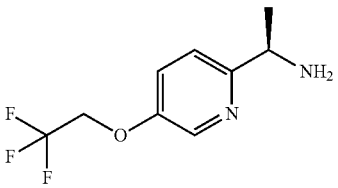
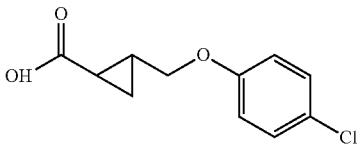
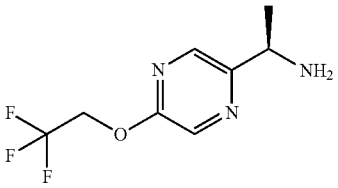
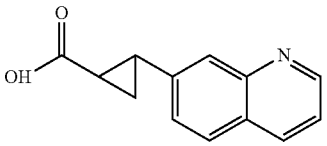
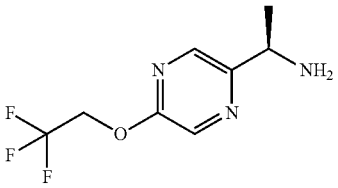
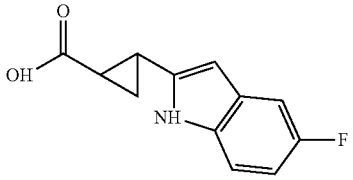
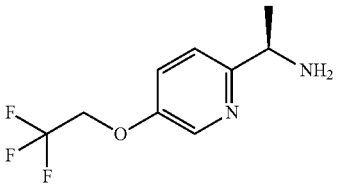
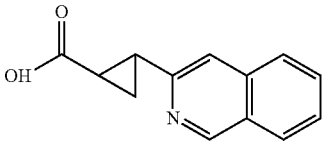
Example 165			411.1	1.84 min	HPLC
Example 166			414.1	1.55 min	HPLC
Example 167			418.0	1.74 min	HPLC
Example 168			420.1	1.65 min	HPLC
Example 169			427.1	1.80 min	HPLC
Example 170			415.2	1.62 min	HPLC
Example 171			421.1	1.78 min	HPLC
Example 172			414.2	1.66 min	HPLC

TABLE 3-continued

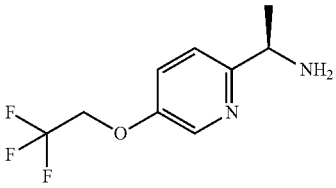
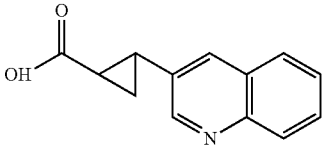
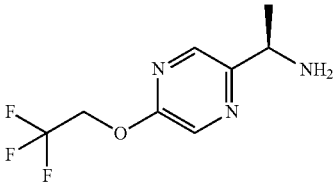
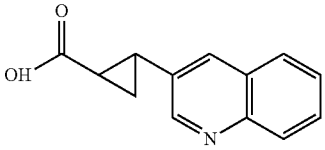
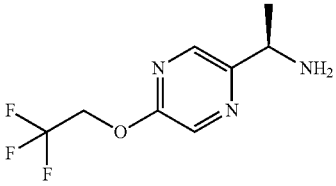
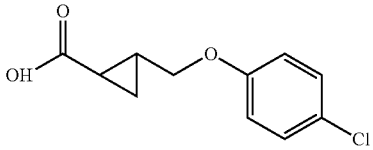
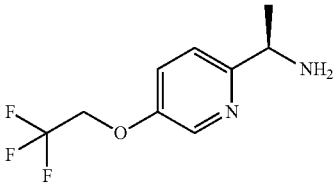
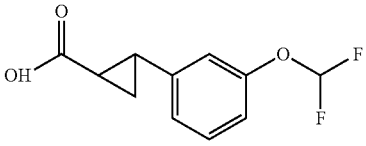
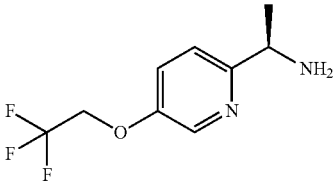
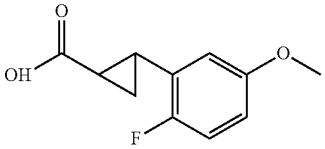
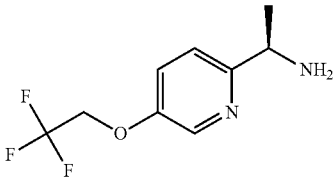
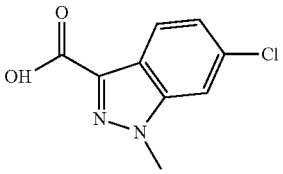
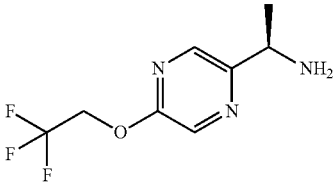
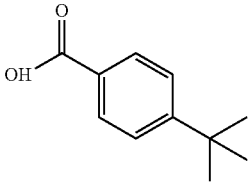
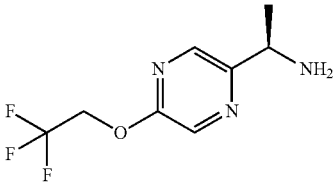
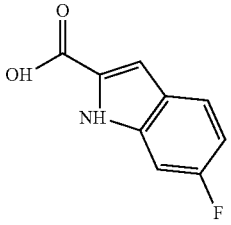
Example 173			414.2	1.58 min	HPLC
Example 174			415.1	1.64 min	HPLC
Example 175			428.1	1.87 min	HPLC
Example 176			429.1	1.72 min	HPLC
Example 177			411.1	1.71 min	HPLC
Example 178			411.1	1.88 min	HPLC
Example 179			380.2	1.96 min	HPLC
Example 180			381.1	1.75 min	HPLC

TABLE 3-continued

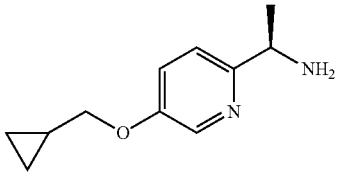
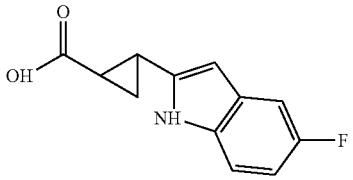
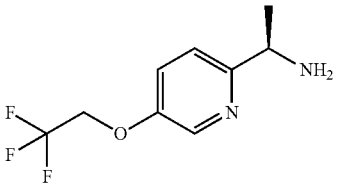
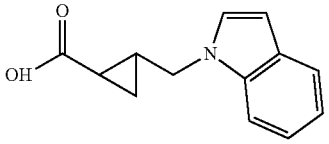
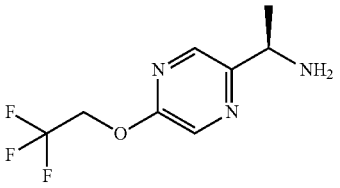
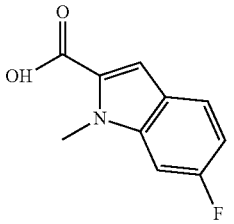
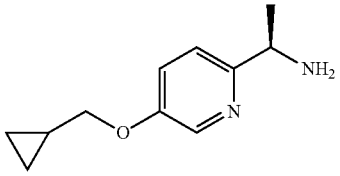
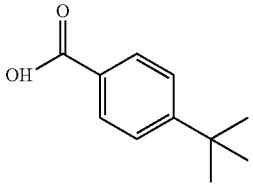
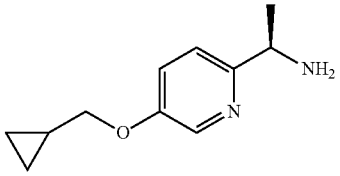
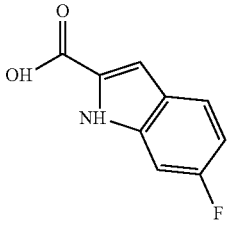
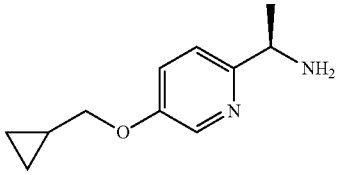
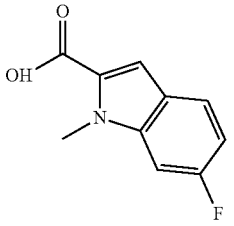
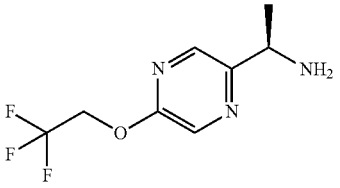
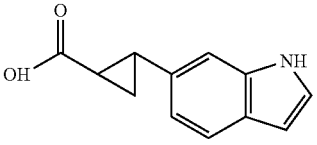
Example 181			392.2	1.74 min	HPLC
Example 182			416.1	1.75 min	HPLC
Example 183			1.88 min	1.88 min	HPLC
Example 184			353.0	1.94 min	HPLC
Example 185			352.2	1.72 min	HPLC
Example 186			366.1	1.85 min	HPLC
Example 187			403.1	1.69 min	HPLC

TABLE 3-continued

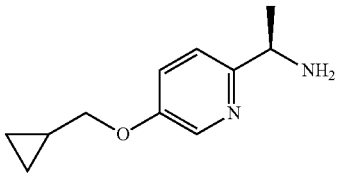
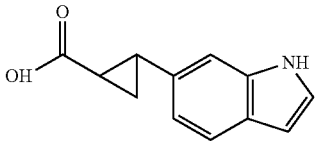
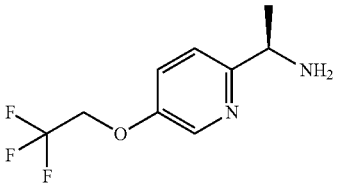
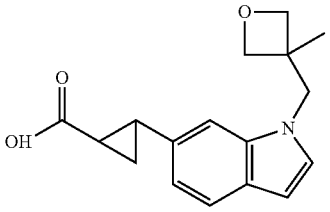
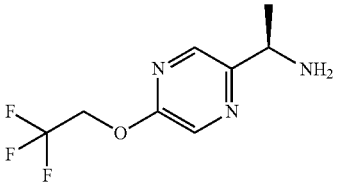
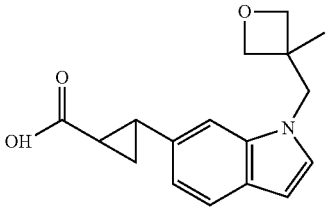
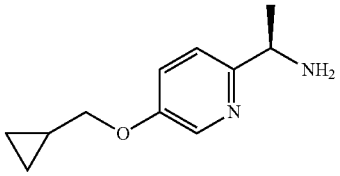
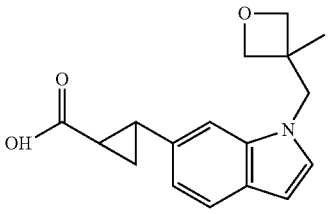
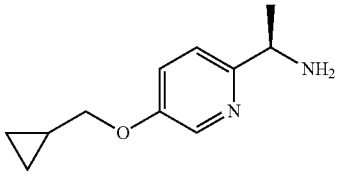
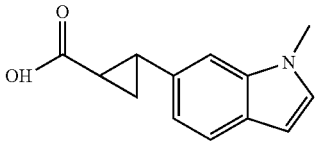
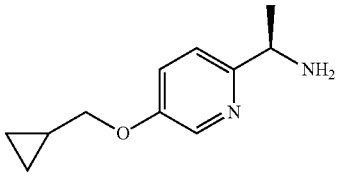
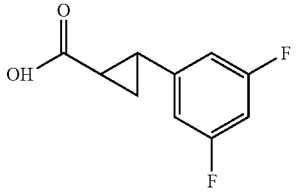
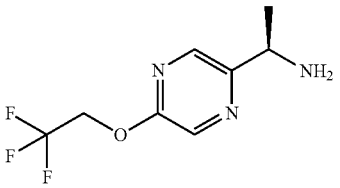
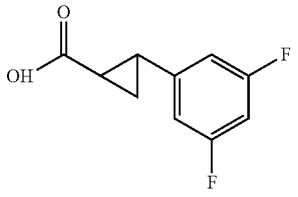
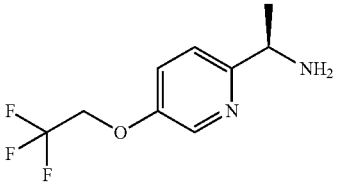
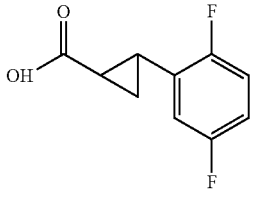
Example 188			374.1	1.65 min	HPLC
Example 189			487.9	1.70 min	HPLC
Example 190			487.1	1.77 min	HPLC
Example 191			460.0	1.73 min	HPLC
Example 192			390.0	1.77 min	HPLC
Example 193			371.1	1.78 min	HPLC
Example 194			400.0	1.88 min	HPLC
Example 195			399.1	1.78 min	HPLC

TABLE 3-continued

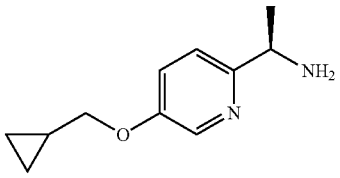
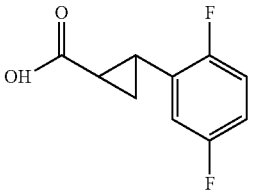
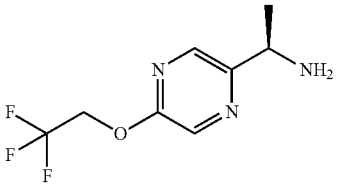
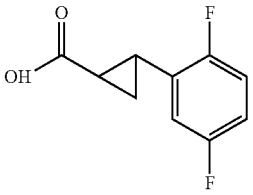
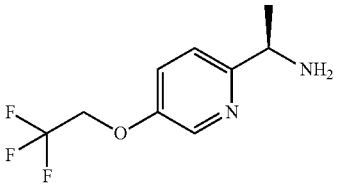
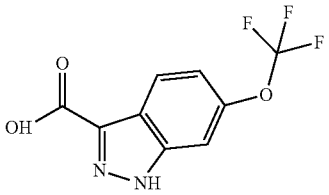
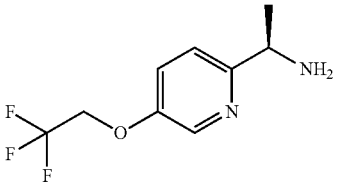
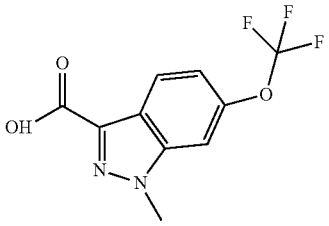
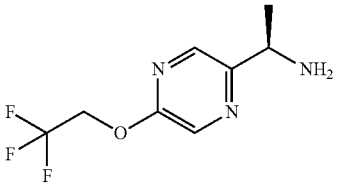
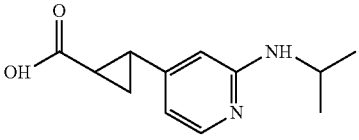
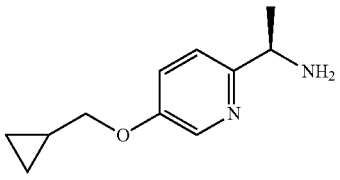
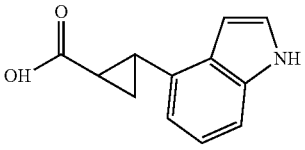
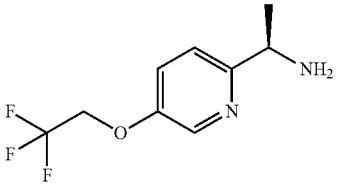
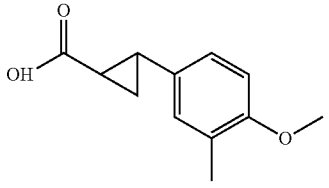
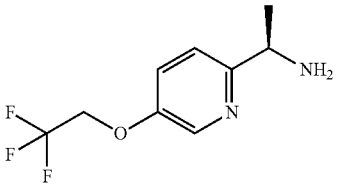
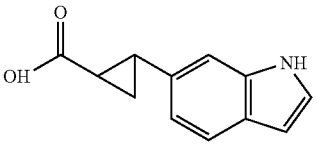
Example 196			371.1	1.77 min	HPLC
Example 197			400.0	1.81 min	HPLC
Example 198			447.0	1.79 min	HPLC
Example 199			461.0	1.93 min	HPLC
Example 200			422.1	1.64 min	HPLC
Example 201			374.1	1.62 min	HPLC
Example 202			408.8	1.79 min	HPLC
Example 203			Confirmed by NMR (see Table 2)		Chiral-HPLC

TABLE 3-continued

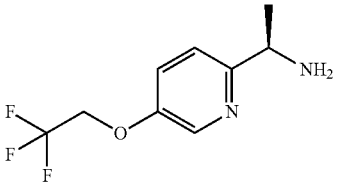
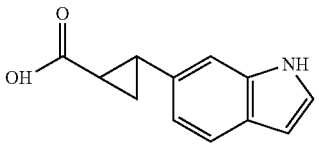
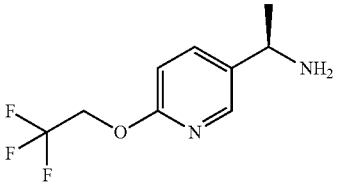
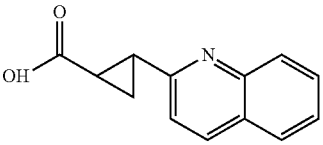
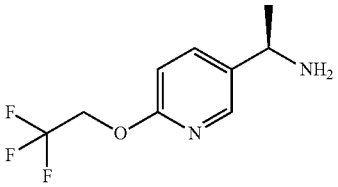
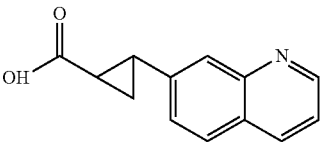
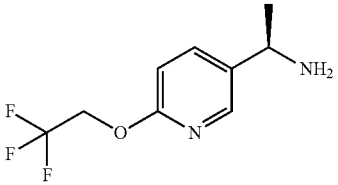
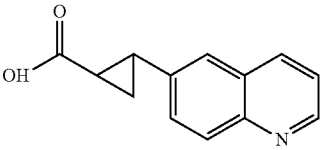
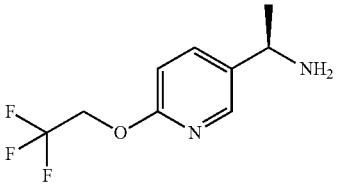
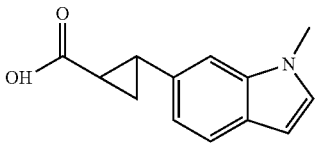
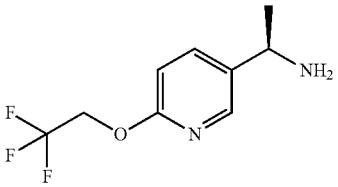
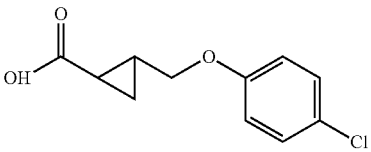
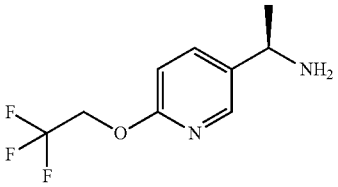
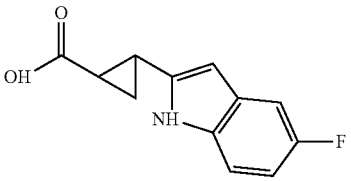
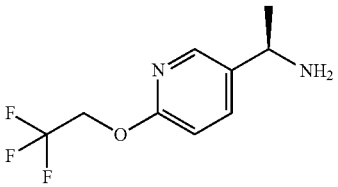
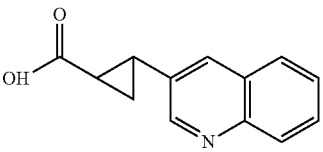
Example 204			Confirmed by NMR (see Table 2)		Chiral-HPLC
Example 205			414.1	1.82 min	HPLC
Example 206			414.1	1.68 min	HPLC
Example 207			414.1	1.66 min	HPLC
Example 208			416.1	1.87 min	HPLC
Example 209			427.0	1.92 min	HPLC
Example 210			420.1	1.83 min	HPLC
Example 211			414.1	1.71 min	HPLC

TABLE 3-continued

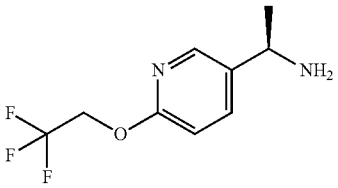
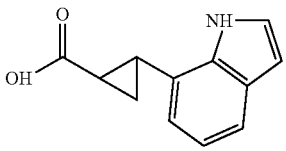
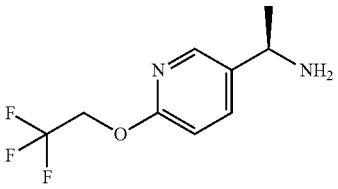
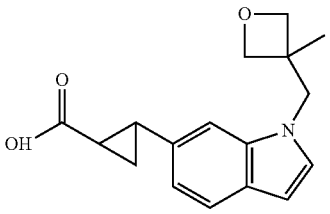
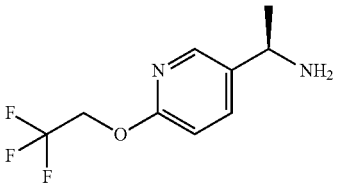
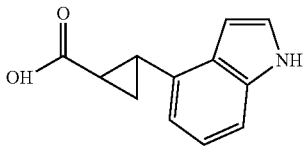
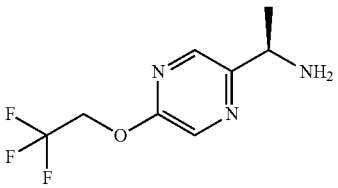
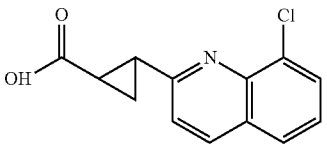
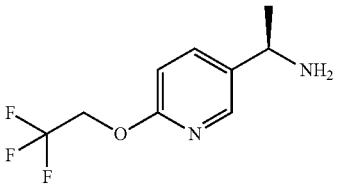
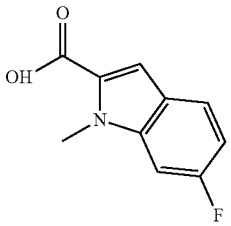
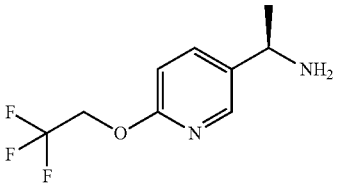
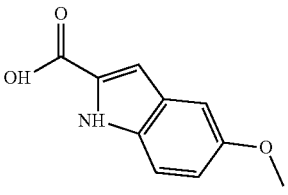
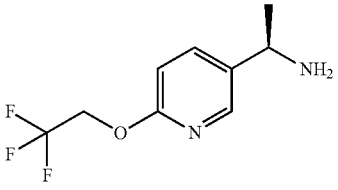
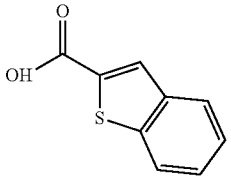
Example 212			402.1	1.84 min	HPLC
Example 213			486.1	1.84 min	HPLC
Example 214			402.1	1.74 min	HPLC
Example 215			Confirmed by NMR (see Table 2)		MPLC
Example 216			394.0	1.93 min	HPLC
Example 217			392.1	1.74 min	HPLC
Example 218			379.0	1.88 min	HPLC

TABLE 3-continued

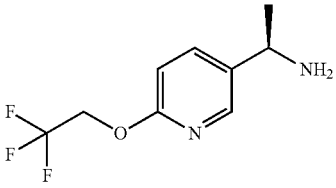
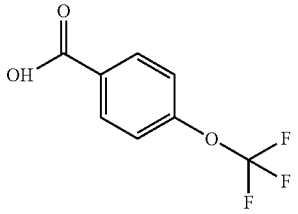
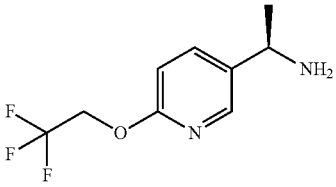
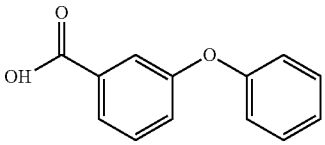
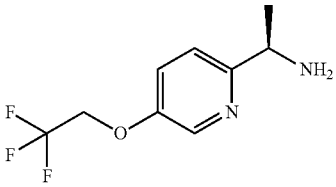
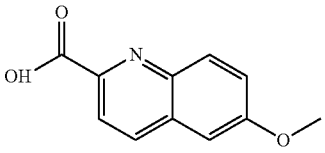
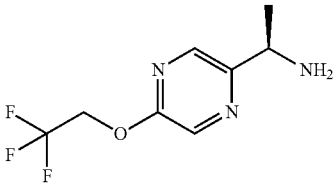
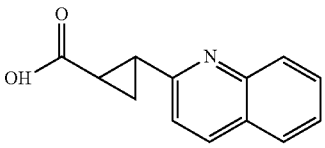
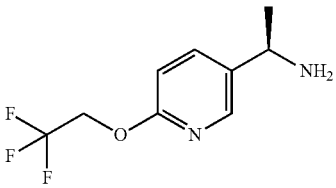
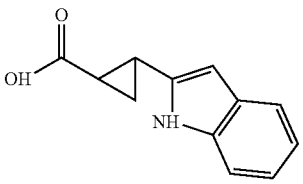
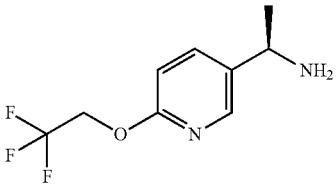
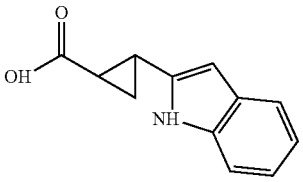
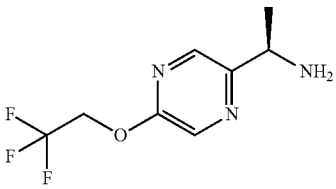
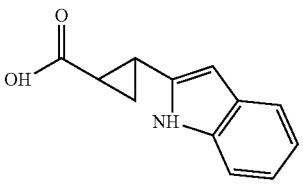
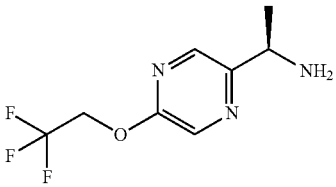
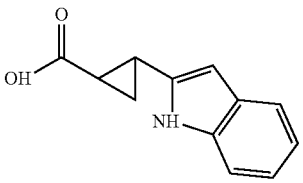
Example 219			407.0	1.91 min	HPLC
Example 220			415.0	1.97 min	HPLC
Example 221			405.8	1.85 min	HPLC
Example 222			Confirmed by NMR (see Table 2)		Chiral-HPLC
Example 223			Confirmed by NMR (see Table 2)		Chiral-HPLC
Example 224			Confirmed by NMR (see Table 2)		Chiral-HPLC
Example 225			Confirmed by NMR (see Table 2)		MPLC
Example 226			Confirmed by NMR (see Table 2)		MPLC

TABLE 3-continued

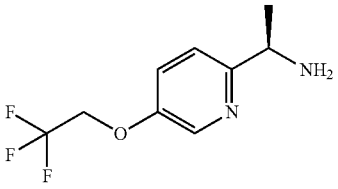
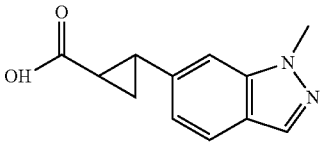
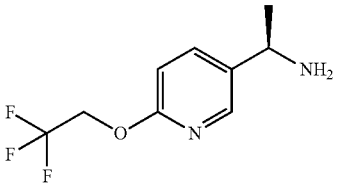
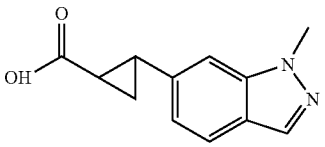
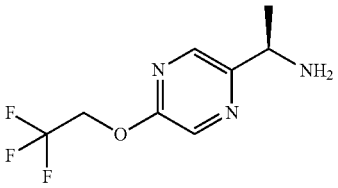
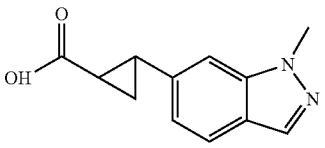
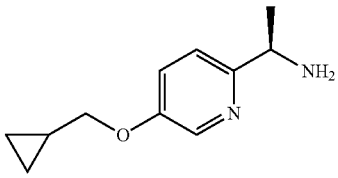
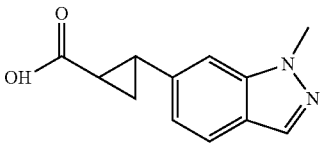
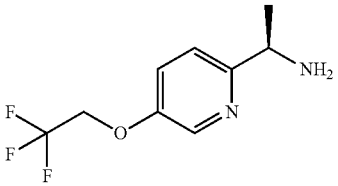
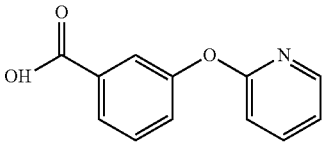
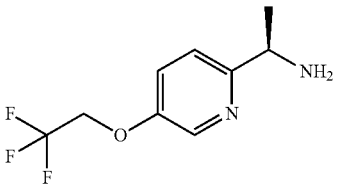
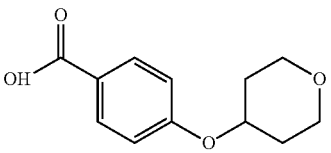
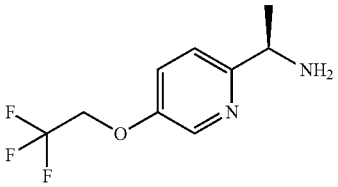
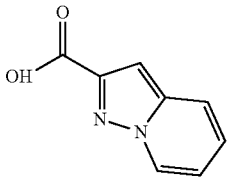
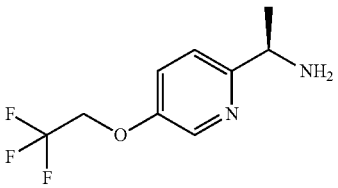
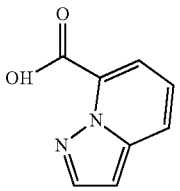
Example 227			Confirmed by NMR (see Table 2)		Chiral-HPLC
Example 228			417.1	1.69 min	HPLC
Example 229			418.1	1.64 min	HPLC
Example 230			389.2	1.59 min	HPLC
Example 231			416.1	1.66 min	HPLC
Example 232			423.1	1.61 min	HPLC
Example 233			363.1	1.60 min	HPLC
Example 234			363.0	1.76 min	HPLC

TABLE 3-continued

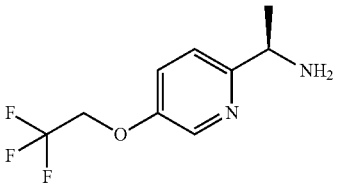
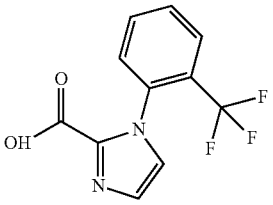
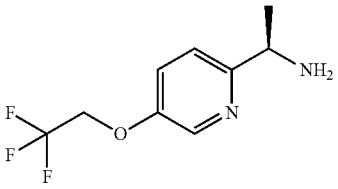
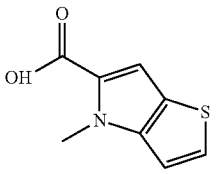
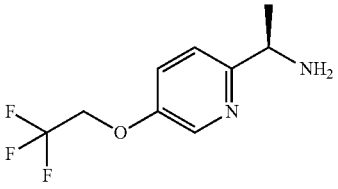
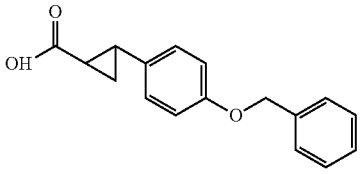
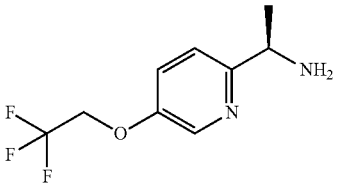
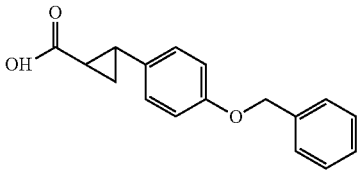
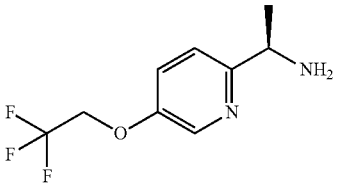
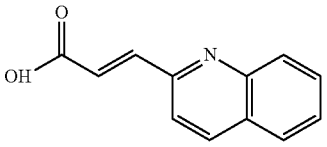
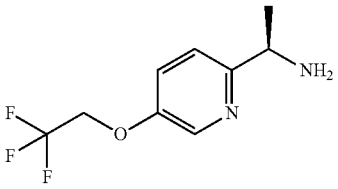
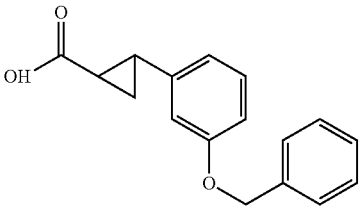
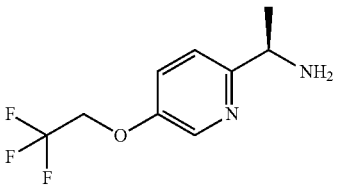
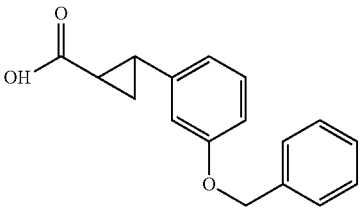
Example 235			457.1	1.78 min	HPLC
Example 236			382.1	1.75 min	HPLC
Example 237			Confirmed by NMR (see Table 2)		MPLC
Example 238			Confirmed by NMR (see Table 2)		MPLC
Example 239			400.1	1.62 min	HPLC
Example 240			Confirmed by NMR (see Table 2)		MPLC
Example 241			Confirmed by NMR (see Table 2)		MPLC
Example 242	Alternative route		378.9	1.48 min	HPLC

TABLE 3-continued

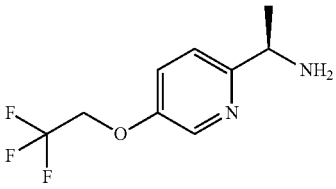
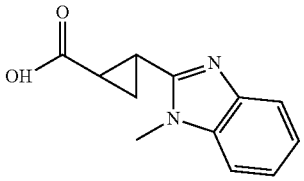
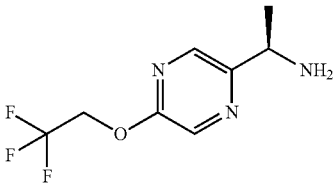
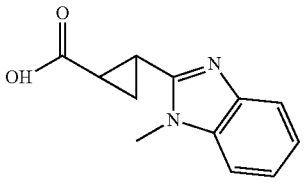
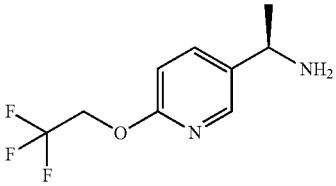
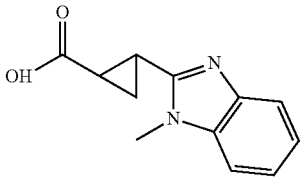
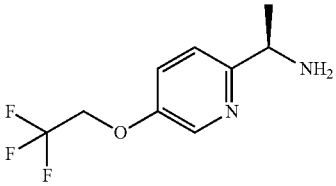
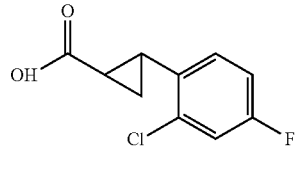
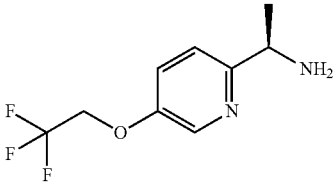
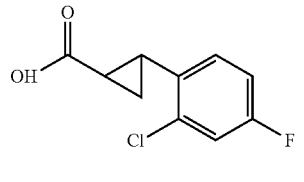
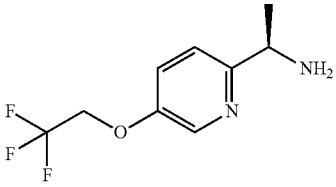
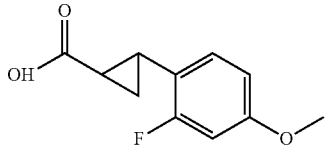
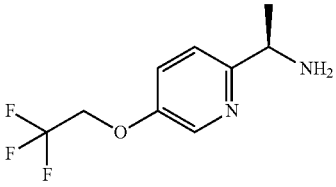
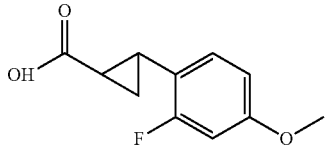
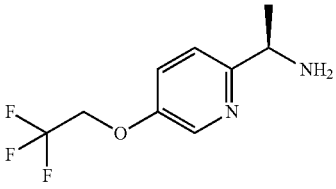
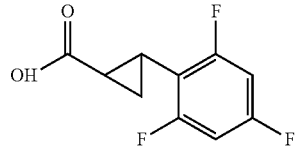
Example 243			416.9	1.52 min	HPLC
Example 244			418.0	1.58 min	HPLC
Example 245			416.9	1.64 min	HPLC
Example 246			414.9	1.81 min	MPLC
Example 247			414.9	1.79 min	MPLC
Example 248			411.0	1.73 min	MPLC
Example 249			411.0	1.72 min	MPLC
Example 250			416.9	1.78 min	MPLC

TABLE 3-continued

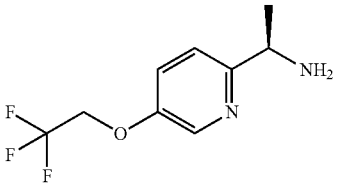
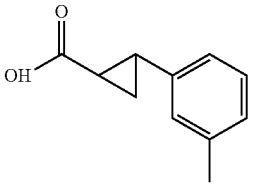
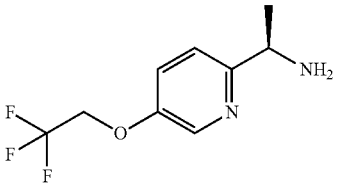
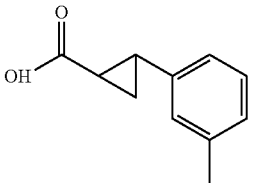
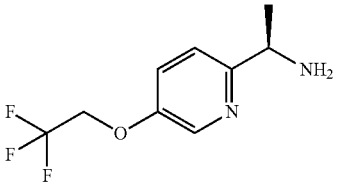
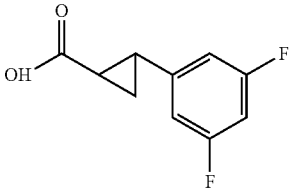
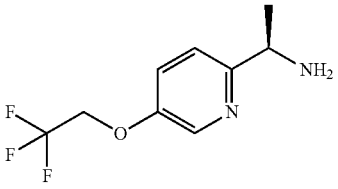
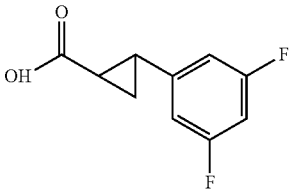
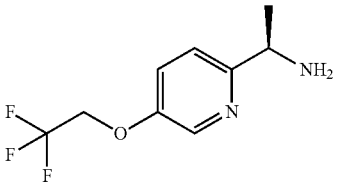
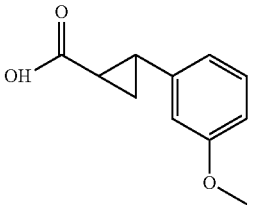
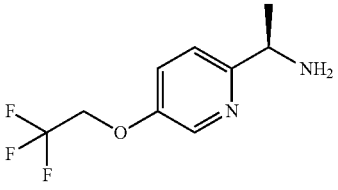
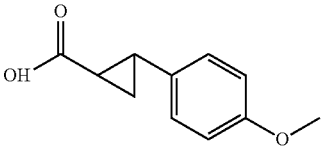
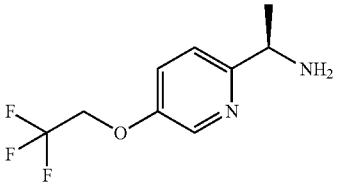
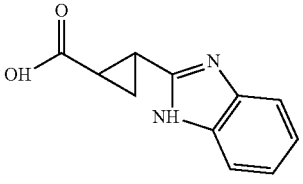
Example 251			377.0	1.80 min	MPLC
Example 252			377.0	1.80 min	MPLC
Example 253			399.0	1.77 min	MPLC
Example 254			399.0	1.77 min	MPLC
Example 255	Alternative route		379.0	1.51 min	HPLC
Example 256	Alternative route		539.9	1.66 min	HPLC
Example 257	Alternative route		539.9	1.68 min	HPLC
Example 258			393.0	1.71 min	MPLC
Example 259			393.0	1.69 min	MPLC
Example 260			403.0	1.44 min	MPLC

TABLE 3-continued

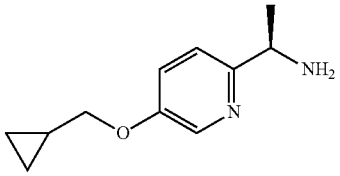
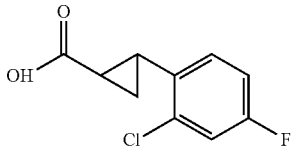
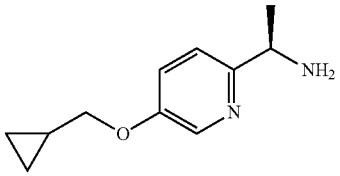
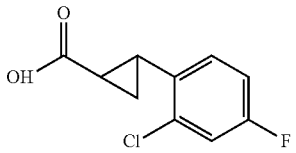
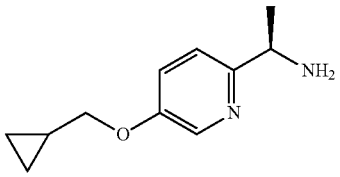
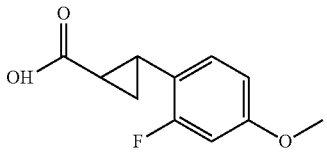
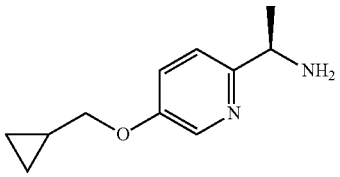
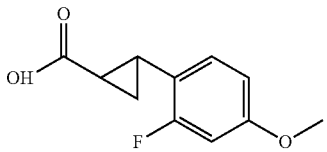
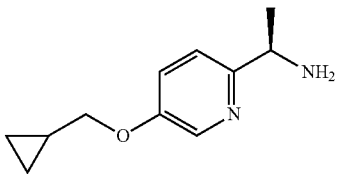
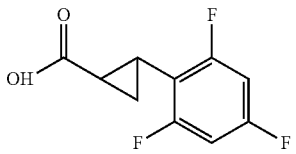
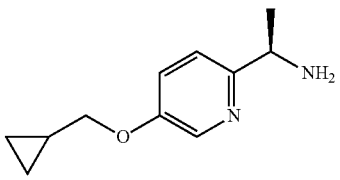
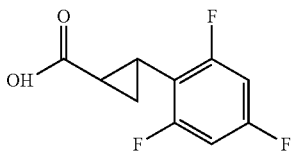
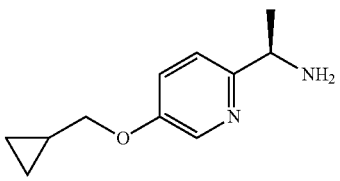
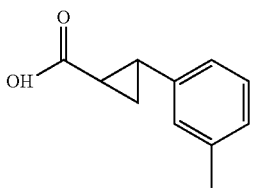
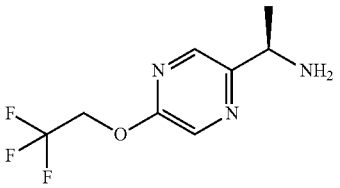
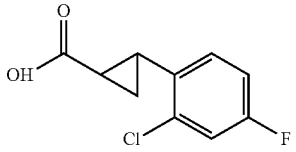
Example 261			387.0	1.85 min	MPLC
Example 262			387.0	1.83 min	MPLC
Example 263			383.1	1.76 min	MPLC
Example 264			383.1	1.75 min	MPLC
Example 265			389.0	1.81 min	MPLC
Example 266			389.0	1.82 min	MPLC
Example 267			349.1	1.83 min	MPLC
Example 268			415.9	1.89 min	MPLC

TABLE 3-continued

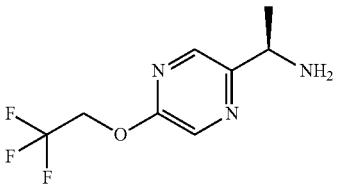
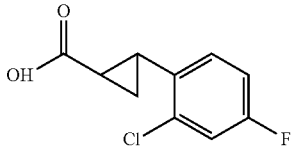
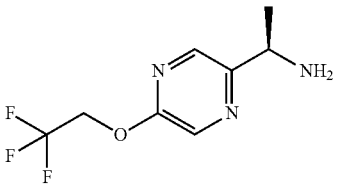
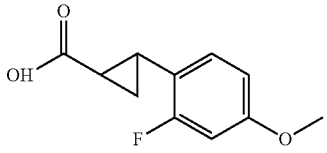
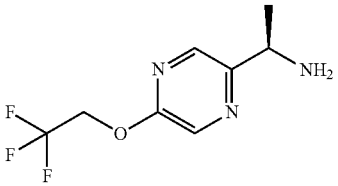
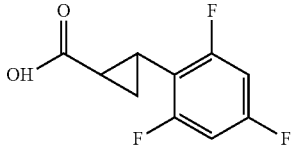
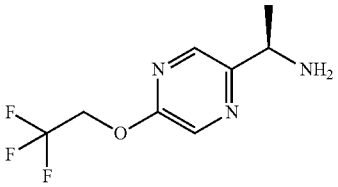
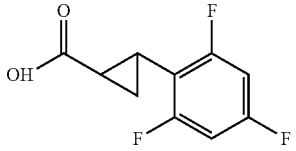
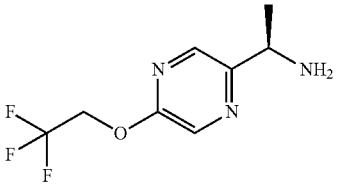
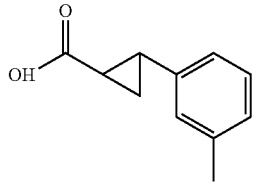
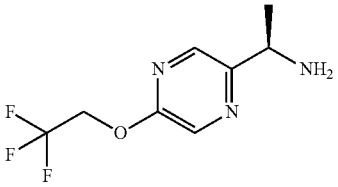
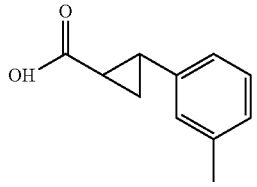
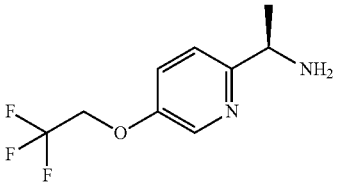
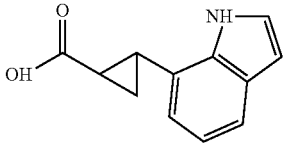
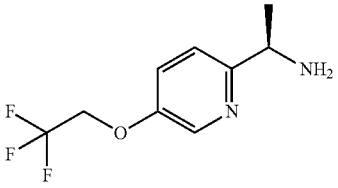
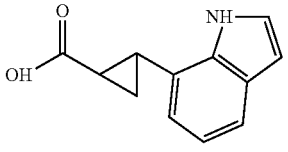
Example 269			415.9	1.87 min	MPLC
Example 270			412.0	1.80 min	MPLC
Example 271			417.9	1.86 min	MPLC
Example 272			418.0	1.85 min	MPLC
Example 273			378.1	1.88 min	MPLC
Example 274			378.1	1.87 min	MPLC
Example 275			402.0	1.75 min	Chiral-HPLC
Example 276			402.0	1.73 min	Chiral-HPLC

TABLE 3-continued

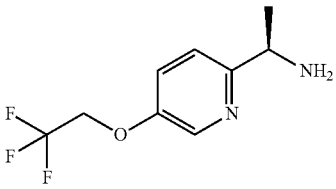
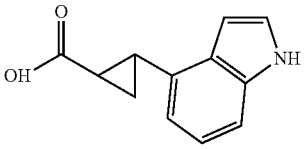
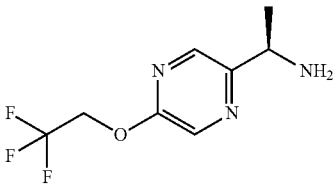
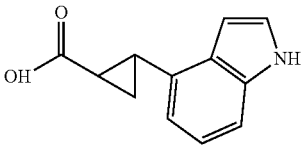
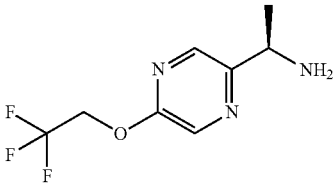
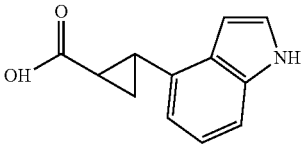
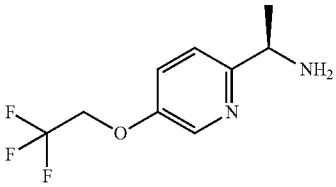
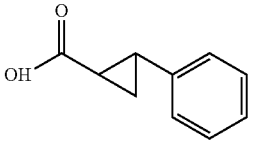
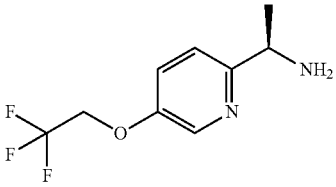
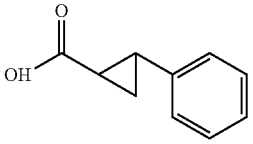
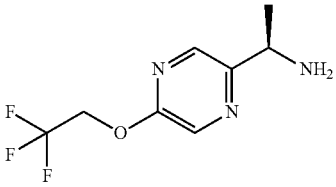
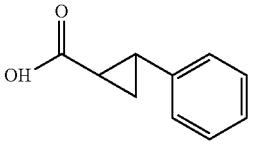
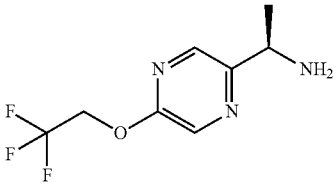
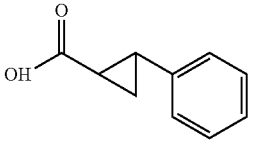
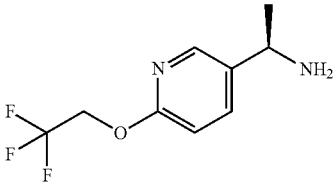
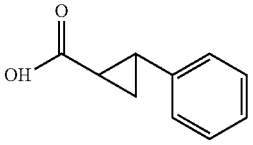
Example 277			402.0	1.62 min	Chiral-HPLC
Example 278			403.0	1.67 min	Chiral-HPLC
Example 279			403.0	1.69 min	Chiral-HPLC
Example 280			363.0	1.72 min	MPLC
Example 281			363.0	1.72 min	MPLC
Example 282			364.0	1.79 min	MPLC
Example 283			364.0	1.79 min	MPLC
Example 284			363.0	1.84 min	MPLC

TABLE 3-continued

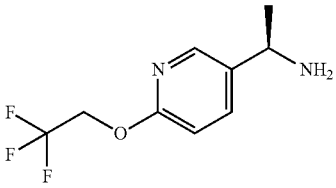
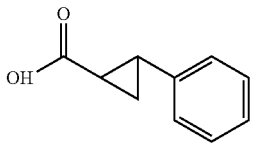
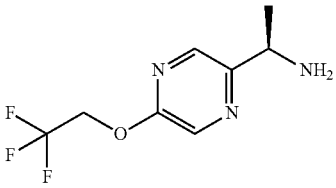
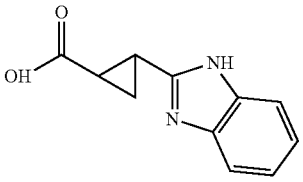
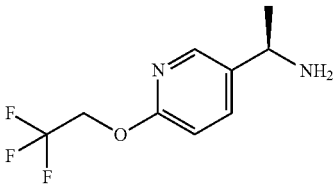
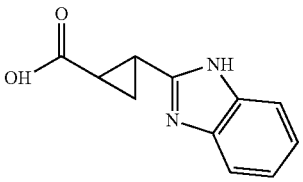
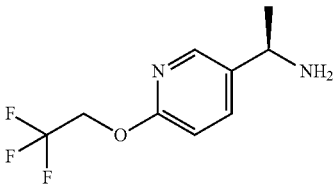
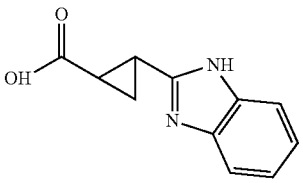
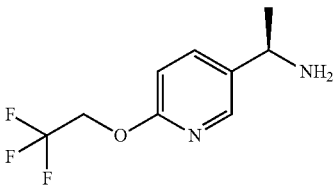
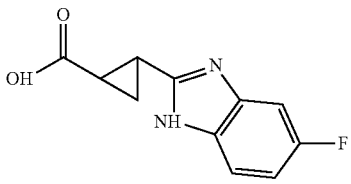
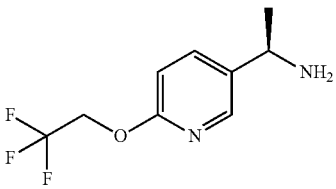
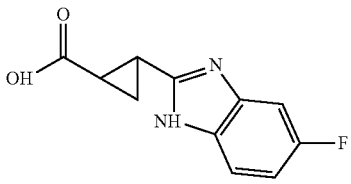
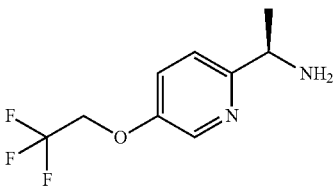
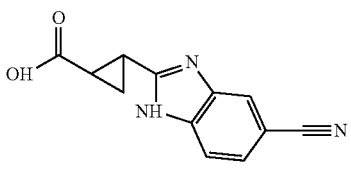
Example 285			363.0	1.83 min	MPLC
Example 286			404.0	1.49 min	MPLC
Example 287			403.0	1.55 min	MPLC
Example 288			403.0	1.56 min	MPLC
Example 289			421.0	1.59 min	MPLC
Example 290			421.0	1.59 min	MPLC
Example 291			428.0	1.44 min	MPLC
Example 292		Alternative route	Confirmed by NMR (see Table 2)		HPLC
Example 293		Alternative route	393.0	1.72 min	HPLC
Example 294		Alternative route	411.0	1.75 min	HPLC
Example 295		Alternative route	418.0	1.66 min	HPLC
Example 296		Alternative route	411.0	1.73 min	HPLC

TABLE 3-continued

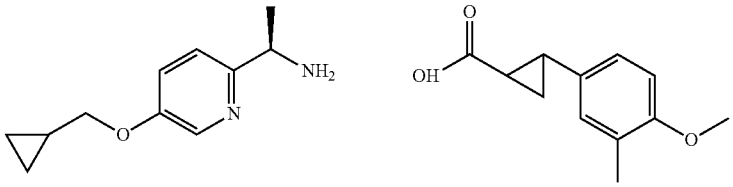
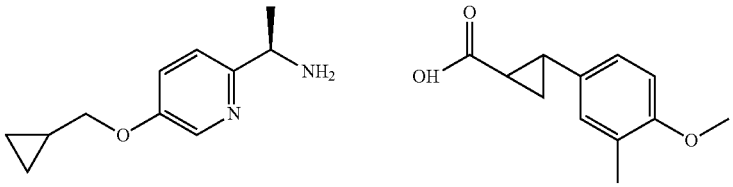
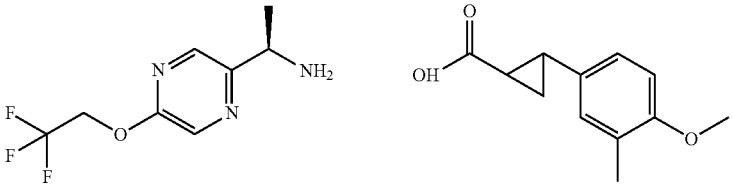
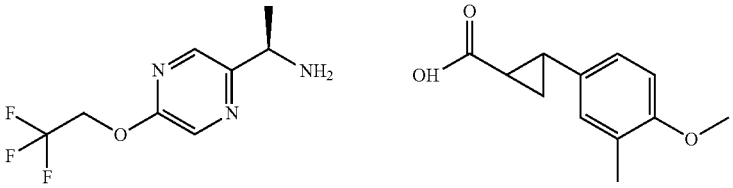
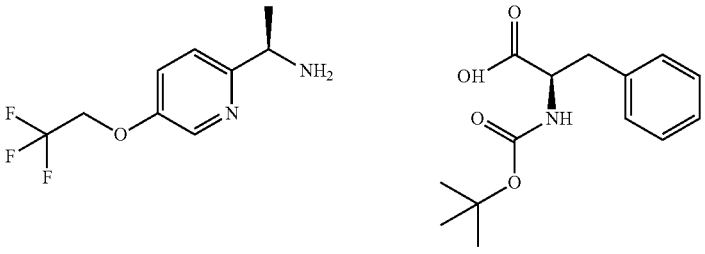
Example 297	Alternative route	418.0	1.63 min	HPLC
Example 298	Alternative route	393.0	1.72 min	HPLC
Exemple 299	Alternative route	411.0	1.75 min	HPLC
Example 300	Alternative route	418.0	1.66 min	HPLC
Example 301	Alternative route	411.0	1.72 min	HPLC
Example 302	Alternative route	418.0	1.63 min	HPLC
Example 303	Alternative route	463.0	1.72 min	HPLC
Example 304	Alternative route	463.0	1.70 min	HPLC
Example 305	Alternative route	470.0	1.68 min	HPLC
Example 306	Alternative route	470.0	1.70 min	HPLC
Example 307		379.1	1.83 min	MPLC
Example 308		379.2	1.83 min	MPLC
Example 309		408.1	1.87 min	MPLC
Example 310		408.0	1.86 min	MPLC
Example 311		467.8	1.81 min	HPLC

TABLE 3-continued

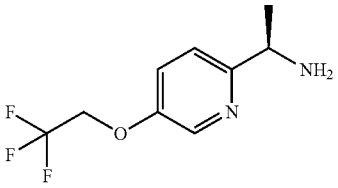
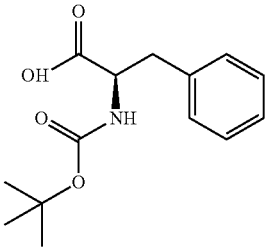
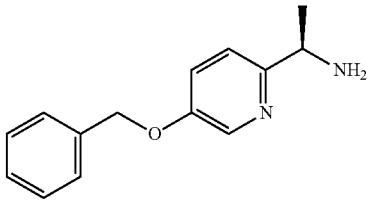
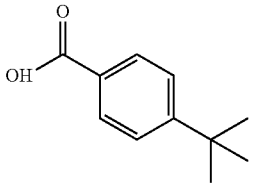
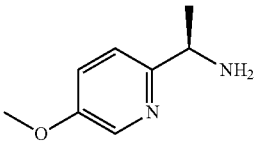
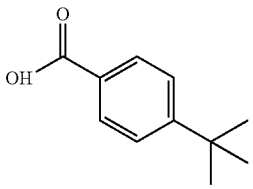
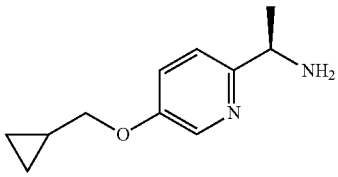
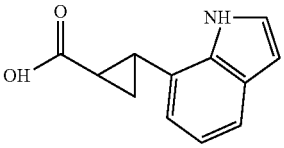
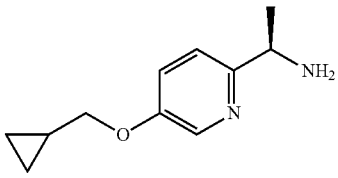
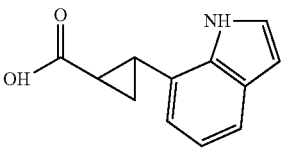
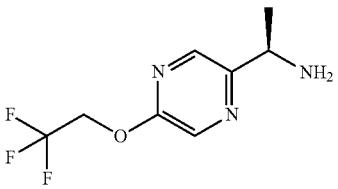
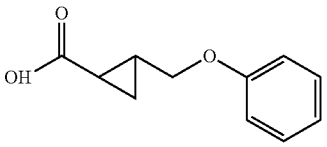
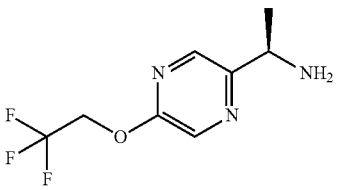
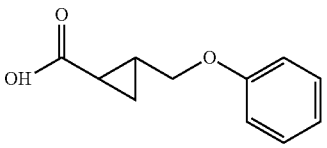
Example 312			467.8	1.82 min	HPLC
Example 313			387.1	2.04 min	HPLC
Example 314	Alternative route		388.1	1.77 min	HPLC
Example 315			311.2	1.78 min	HPLC
Example 316			374.1	1.76 min	Chiral-HPLC
Example 317			374.1	1.78 min	Chiral-HPLC
Example 318			394.0	1.79 min	Chiral-HPLC
Example 319			394.0	1.78 min	Chiral-HPLC

TABLE 3-continued

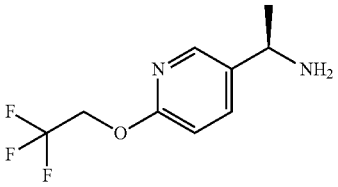
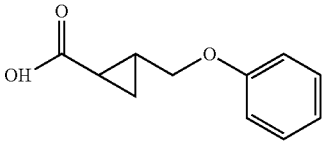
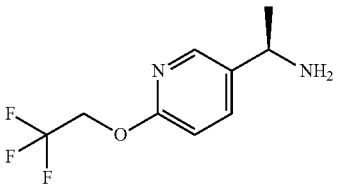
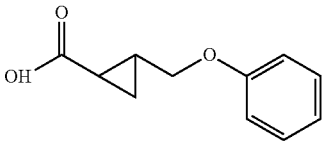
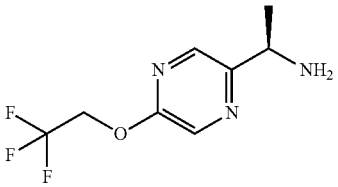
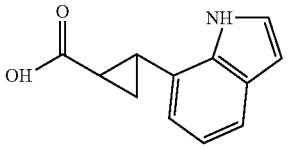
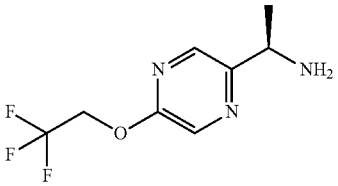
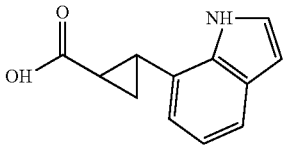
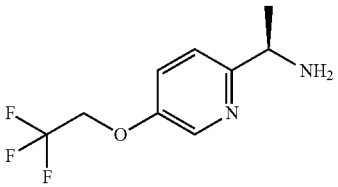
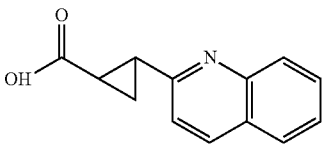
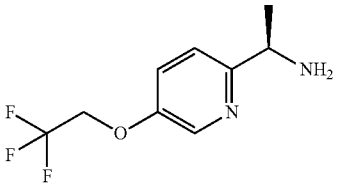
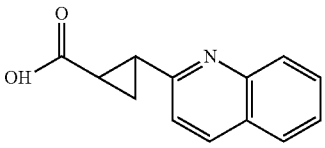
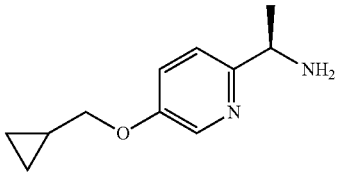
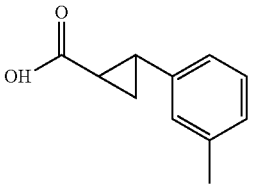
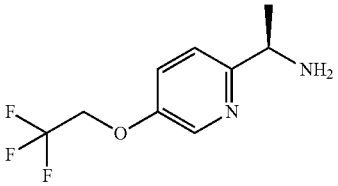
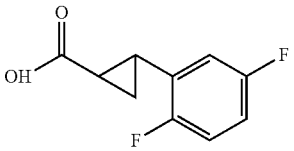
Example 320			393.0	1.83 min	Chiral-HPLC
Example 321			393.0	1.82 min	Chiral-HPLC
Exemple 322			403.0	1.80 min	Chiral-HPLC
Example 323			403.0	1.80 min	Chiral-HPLC
Example 324			414.0	1.70 min	Chiral-HPLC
Example 325			414.0	1.70 min	Chiral-HPLC
Example 326			349.1	1.83 min	MPLC
Example 327			399.0	1.75 min	MPLC

TABLE 3-continued

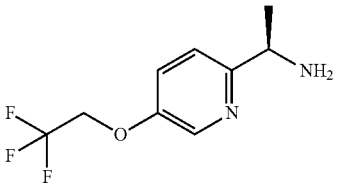
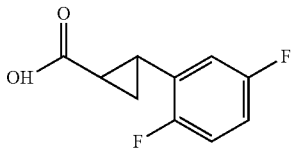
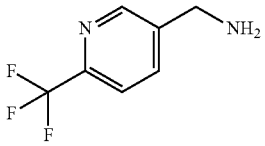
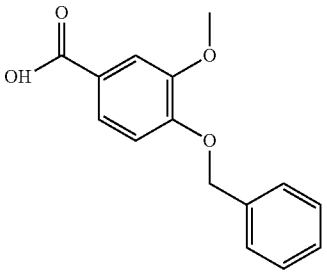
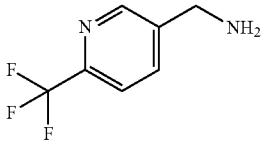
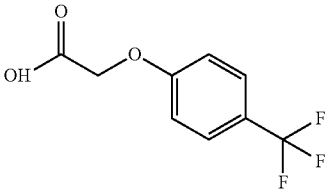
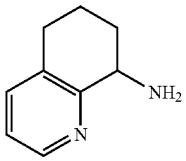
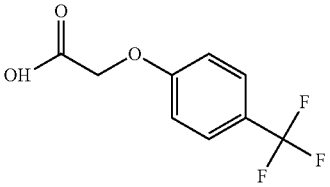
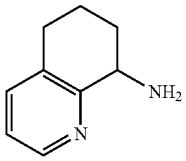
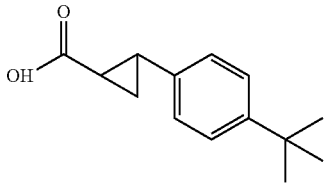
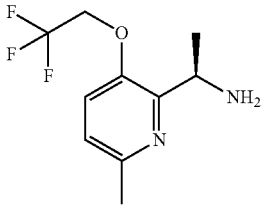
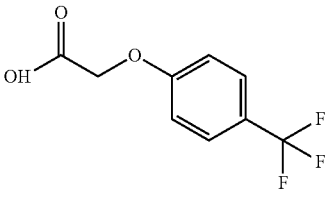
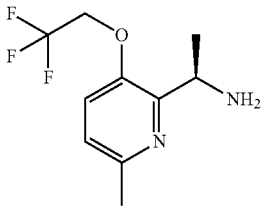
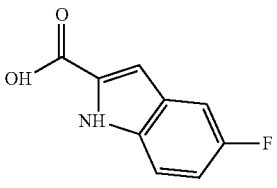
Example 328			399.0	1.74 min	MPLC
Example 329			417.1	3.00 min	HPLC
Example 330			379	2.95 min	HPLC
Example 331			351.1	2,27 min	HPLC
Example 332			349.2	2.45 min	HPLC
Example 333			436.9	1.95 min	HPLC
Example 334			395.9	1.84 min	HPLC

TABLE 3-continued

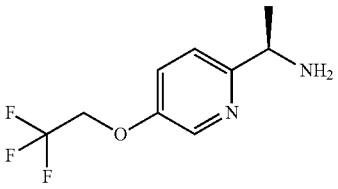
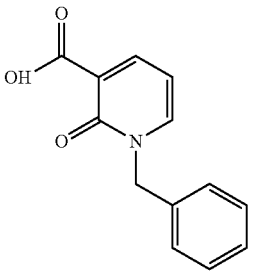
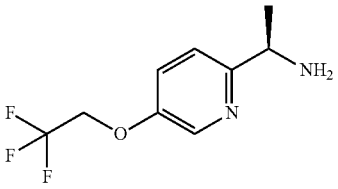
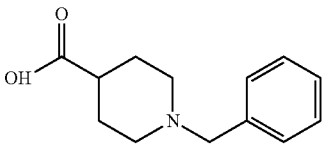
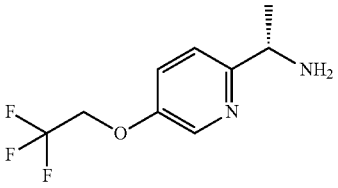
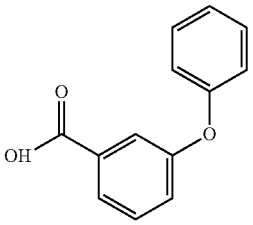
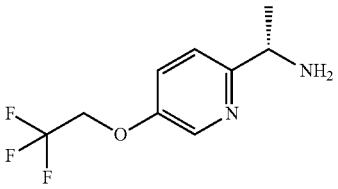
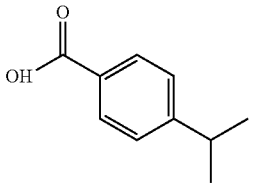
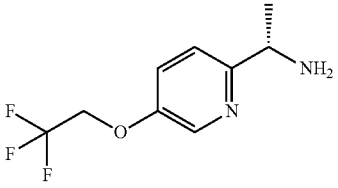
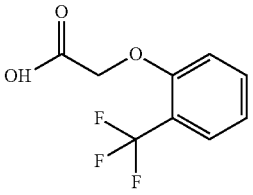
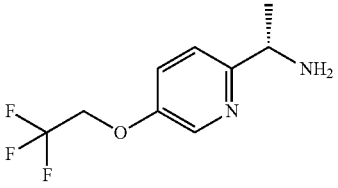
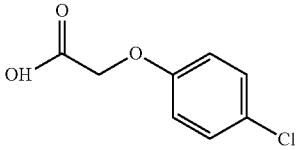
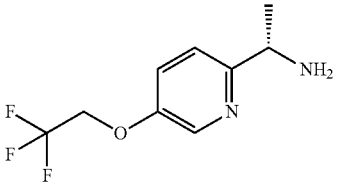
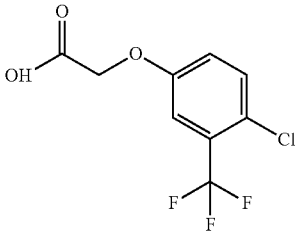
Example 335			430	1.72 min	HPLC
Example 336			420.1	1.52 min	HPLC
Example 337			415	1.88 min	HPLC
Example 338			365.1	1.85 min	HPLC
Example 339			421	1.87 min	HPLC
Example 340			387	1.79 min	HPLC
Example 341			454.9	1.90 min	HPLC

TABLE 3-continued

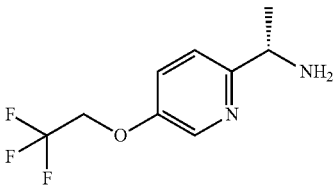
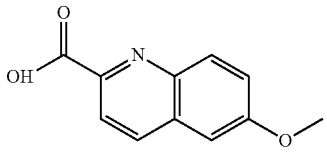
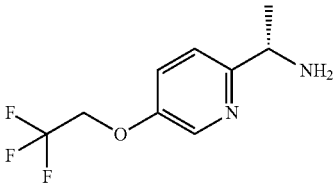
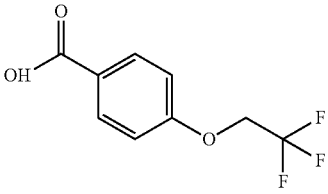
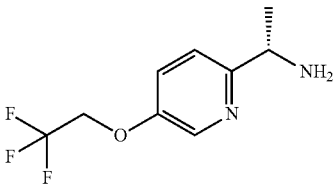
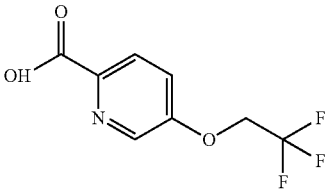
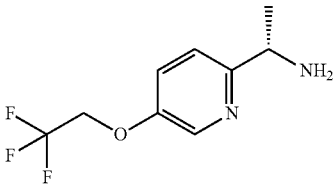
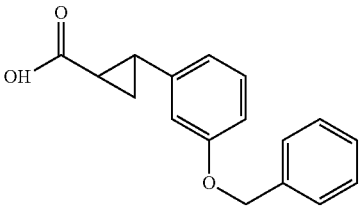
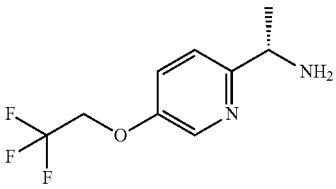
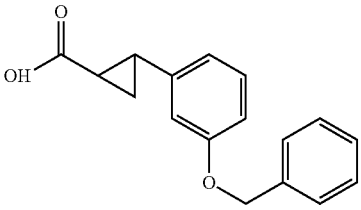
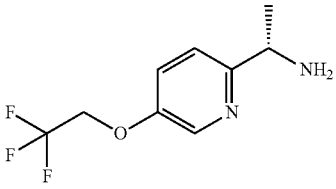
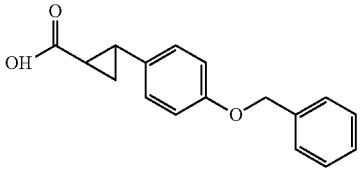
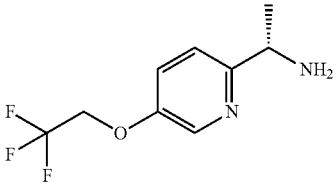
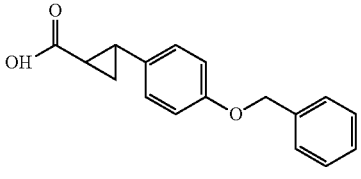
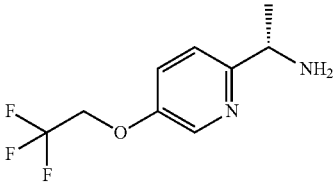
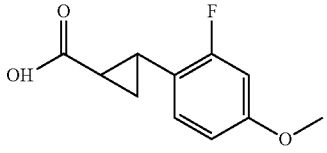
Example 342			405.8	1.84 min	HPLC
Example 343			421	1.74 min	HPLC
Example 344			422	1.79 min	HPLC
Example 345			469.1	1.94 min	MPLC
Example 346			469.1	1.94 min	MPLC
Example 347			469.1	1.93 min	MPLC
Example 348			469.1	1.93 min	MPLC
Example 349			411.1	1.73 min	MPLC

TABLE 3-continued

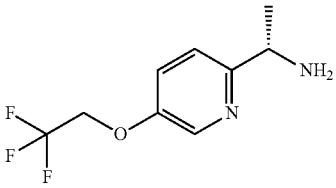
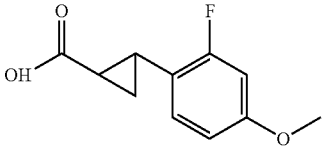
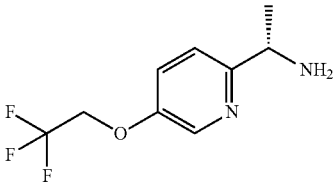
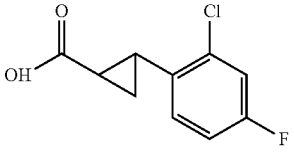
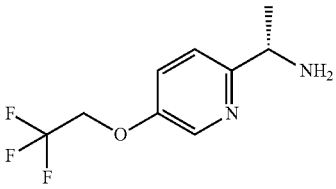
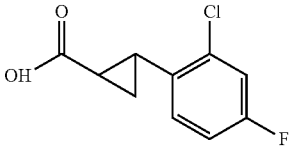
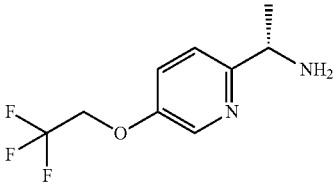
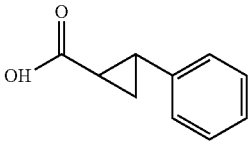
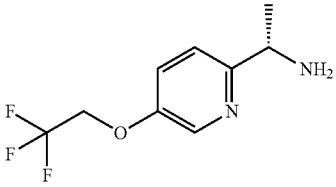
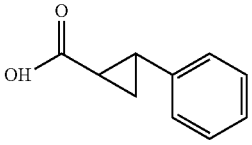
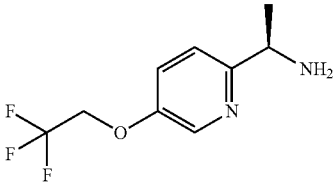
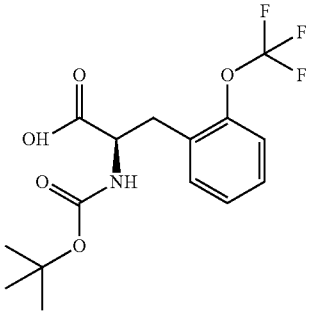
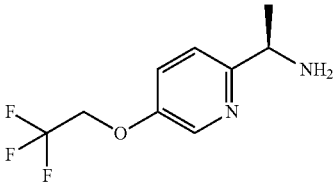
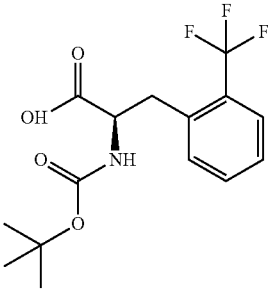
Example 350			411.1	1.72 min	MPLC
Example 351			415	1.81 min	MPLC
Example 352			415	1.79 min	MPLC
Example 353			363.1	1.71 min	MPLC
Example 354			363.1	1.71 min	MPLC
Example 355			552.1	3.42 min	HPLC
Example 356			536.1	3.37 min	HPLC

TABLE 3-continued

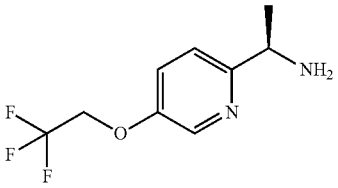
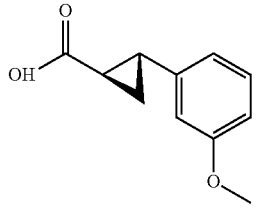
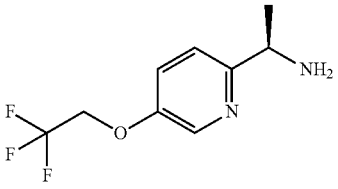
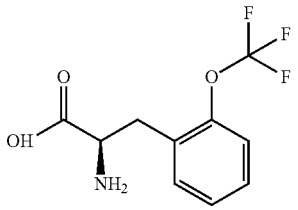
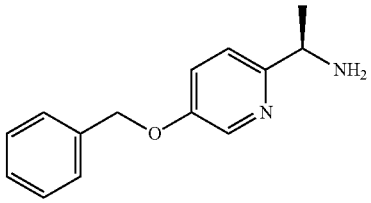
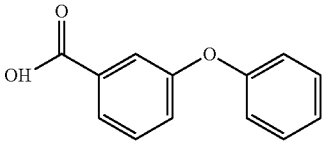
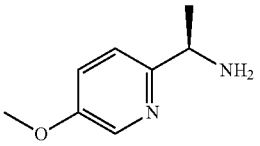
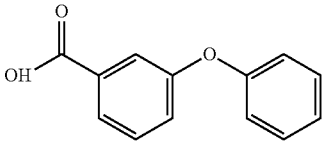
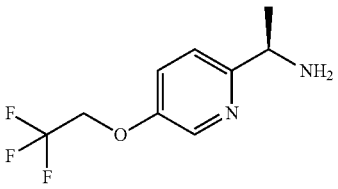
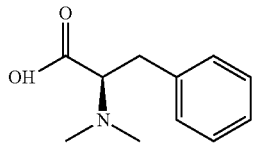
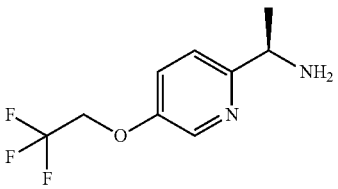
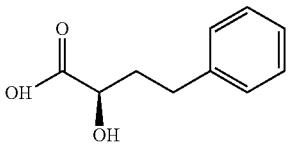
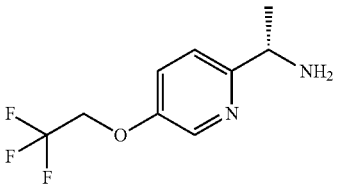
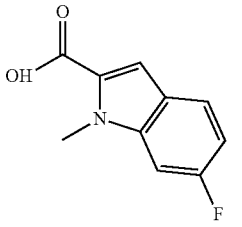
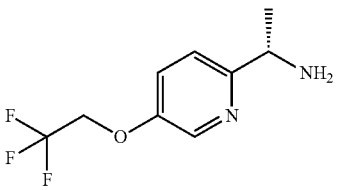
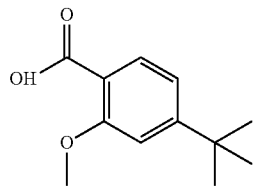
Example 357			Confirmed by NMR (see Table 2)		MPLC
Example 358			450	1.66 min	HPLC
Example 359			423.1	2.00 min	HPLC
Example 360			347.1	1.76 min	HPLC
Example 361			394.2	1.64 min	HPLC
Example 362			381.1	1.64 min	HPLC
Example 363			394.1	1.83 min	HPLC
Example 364			409.1	2.00 min	HPLC

TABLE 3-continued

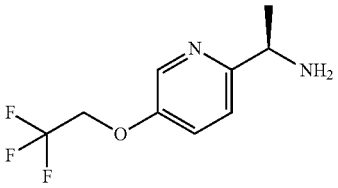
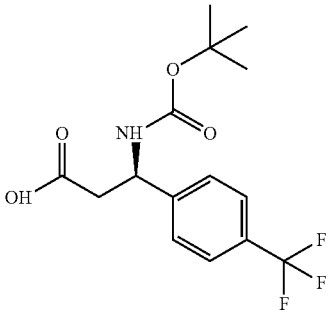
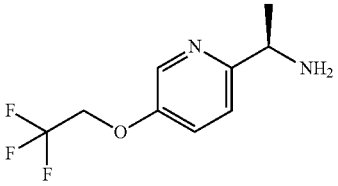
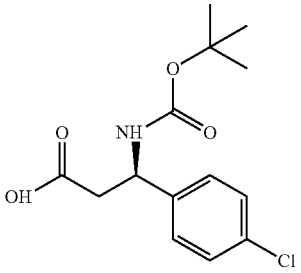
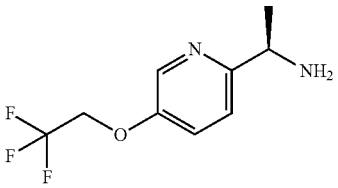
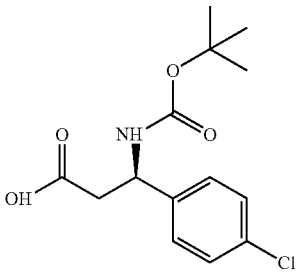
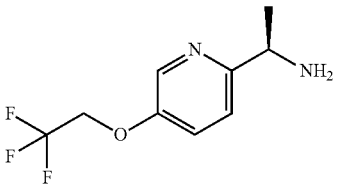
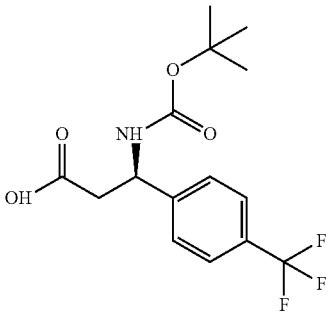
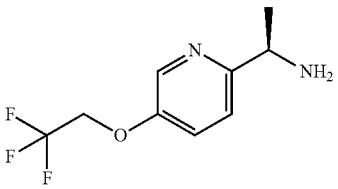
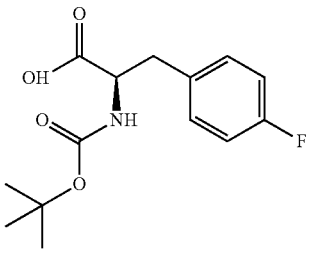
Example 365			534	1.88 min	HPLC
Example 366			500.1	1.84 min	HPLC
Example 367			500	1.82 min	HPLC
Example 368			534.1	1.87 min	HPLC
Example 369			485.8	1.82 min	HPLC

TABLE 3-continued

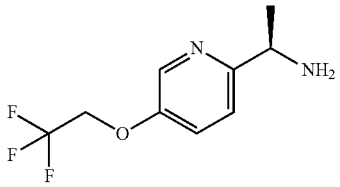
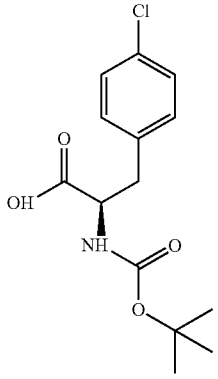
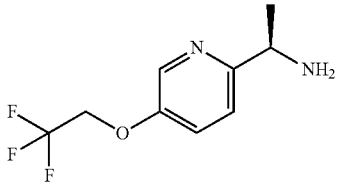
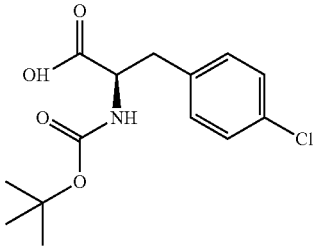
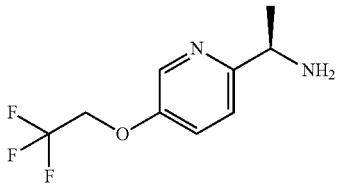
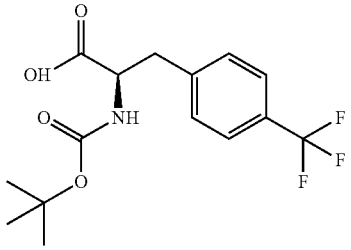
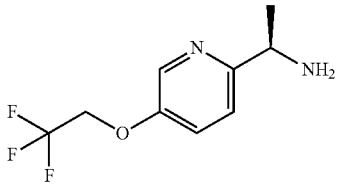
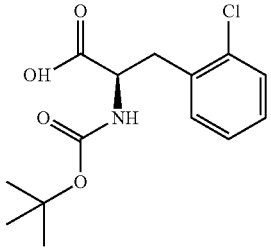
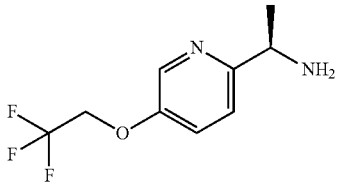
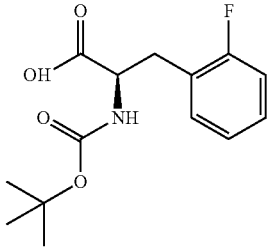
Example 370			501.8	1.90 min	HPLC
Example 371			501.8	1.89 min	HPLC
Example 372			534.1	1.93 min	HPLC
Example 373			501.8	1.89 min	HPLC
Example 374			485.8	1.83 min	HPLC

TABLE 3-continued

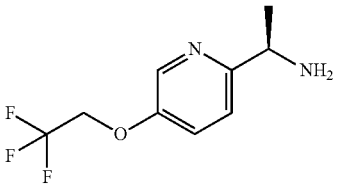
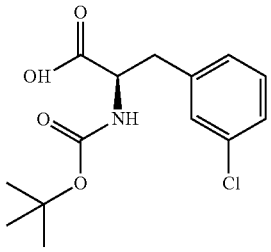
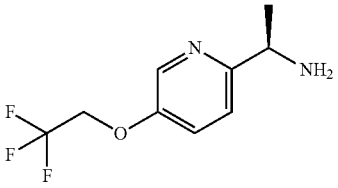
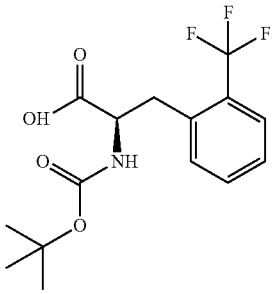
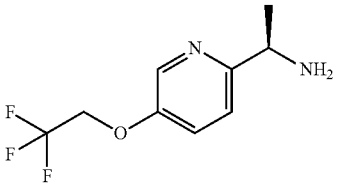
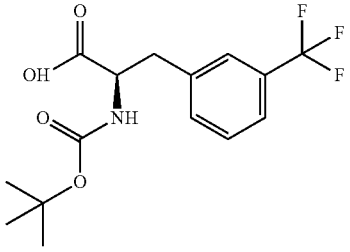
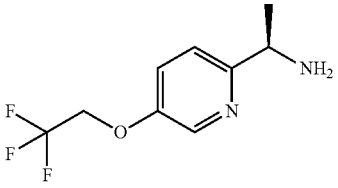
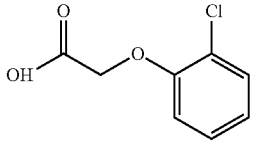
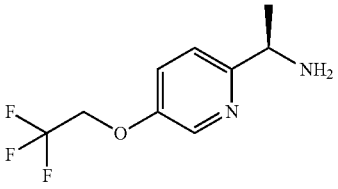
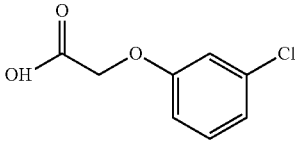
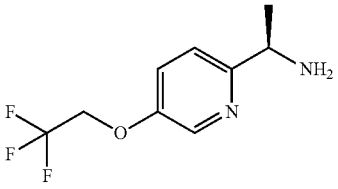
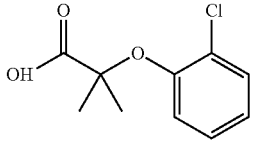
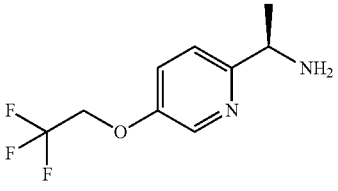
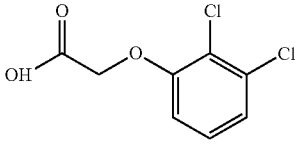
Example 375			500.1	1.90 min	HPLC
Example 376			535.8	1.93 min	HPLC
Example 377			534	1.93 min	HPLC
Example 378			387.1	1.81 min	HPLC
Example 379			387.1	1.79 min	HPLC
Example 380			415.1	1.95 min	HPLC
Example 381			421	1.91 min	HPLC

TABLE 3-continued

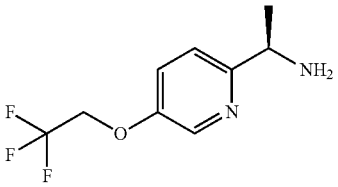
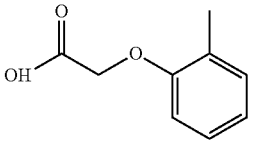
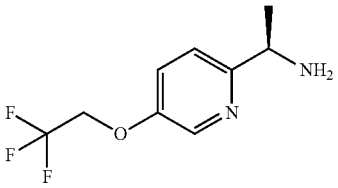
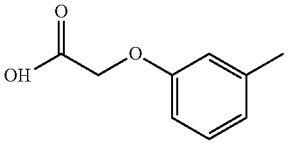
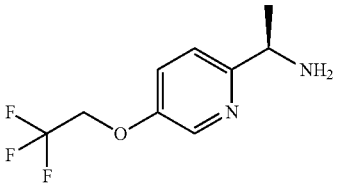
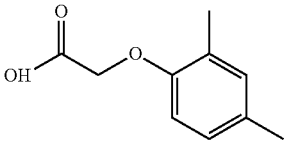
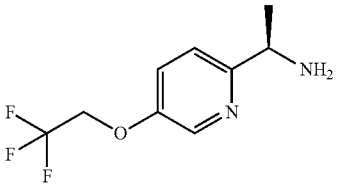
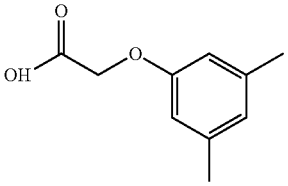
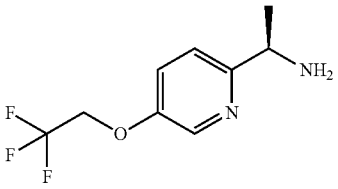
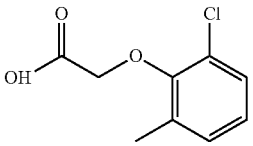
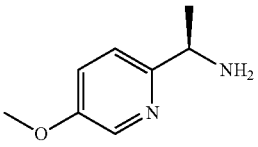
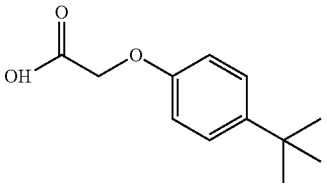
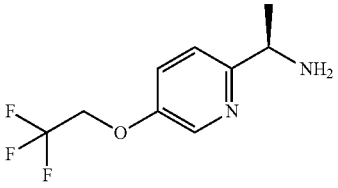
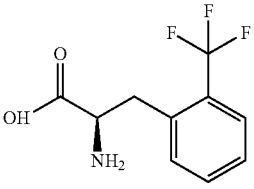
Example 382			367.1	1.83 min	HPLC
Example 383			367.1	1.77 min	HPLC
Example 384			381.2	1.92 min	HPLC
Example 385			381.2	1.87 min	HPLC
Example 386			401.1	1.88 min	HPLC
Example 387			341.1	1.88 min	HPLC
Example 388			434.1	1.62 min	HPLC

TABLE 3-continued

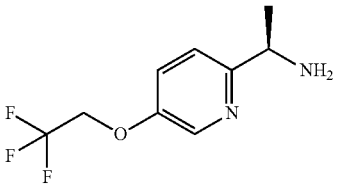
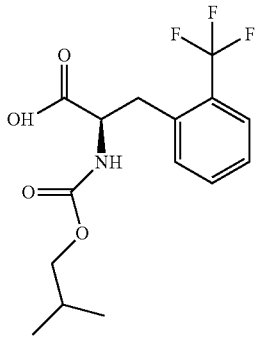
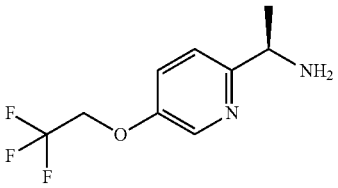
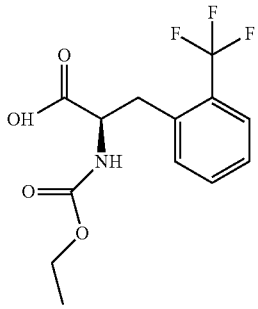
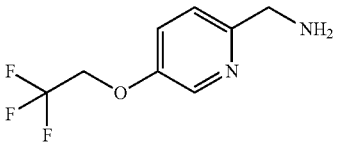
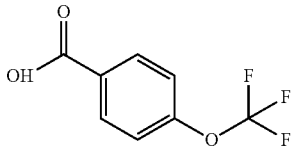
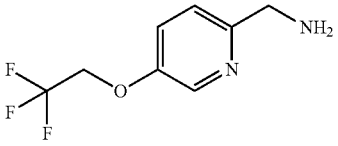
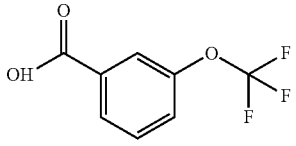
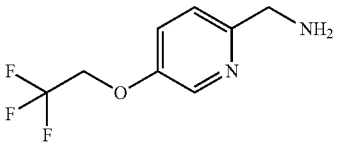
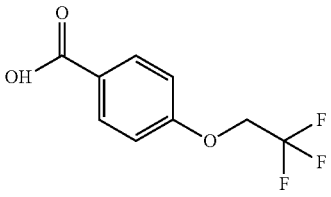
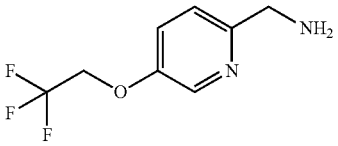
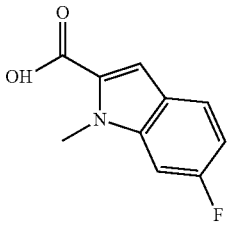
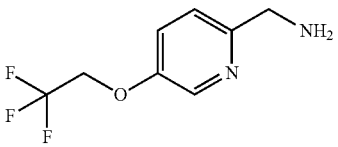
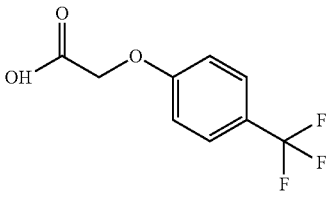
Example 389			535.8	1.92 min	HPLC
Example 390			506	8.11 min	HPLC
Example 391			393.1	1.72 min	HPLC
Example 392			393.1	1.73 min	HPLC
Example 393			407	1.56 min	HPLC
Example 394			380.1	1.73 min	HPLC
Example 395			407.1	1.73 min	HPLC

TABLE 3-continued

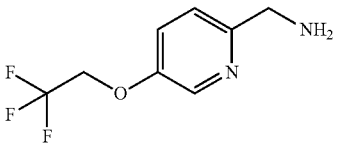
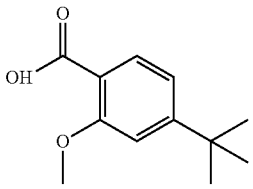
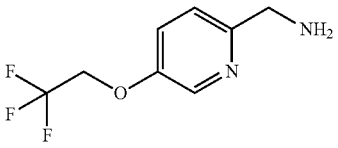
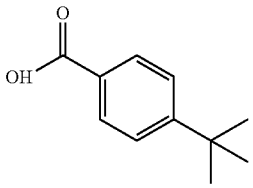
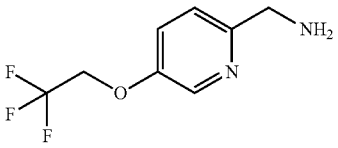
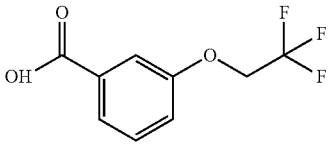
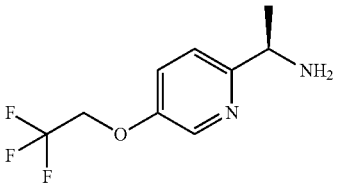
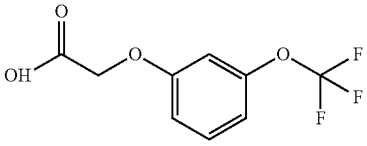
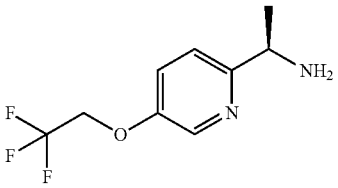
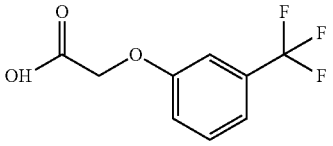
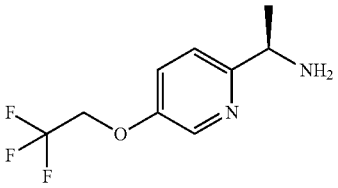
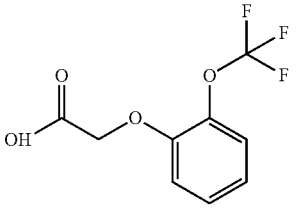
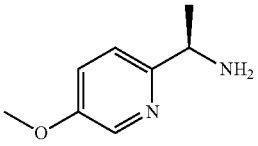
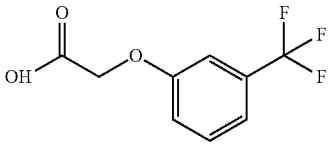
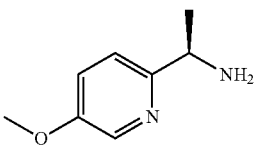
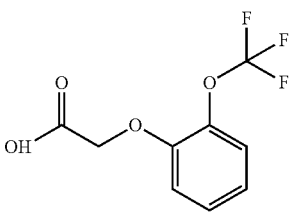
Example 396			395.2	1.89 min	HPLC
Example 397			365.2	1.82 min	HPLC
Example 398			407.1	1.69 min	HPLC
Example 399			437.1	1.85 min	HPLC
Example 400			421.1	1.81 min	HPLC
Example 401			437.1	1.87 min	HPLC
Example 402			353.2	1.68 min	HPLC
Example 403			369.1	1.75 min	HPLC

TABLE 3-continued

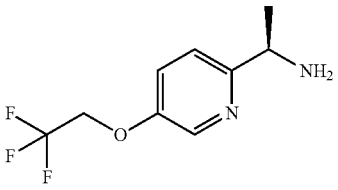
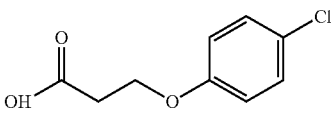
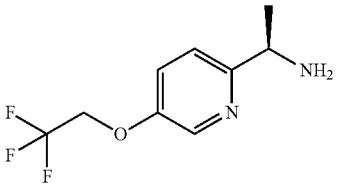
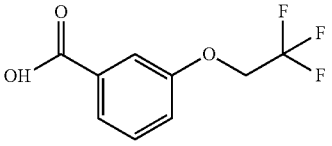
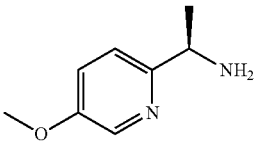
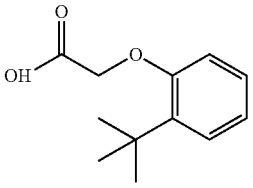
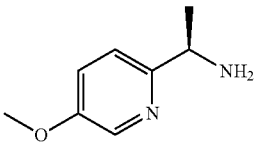
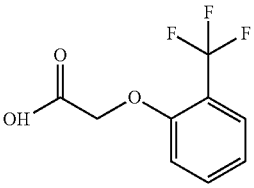
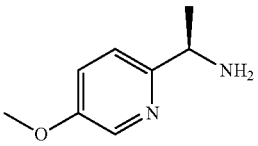
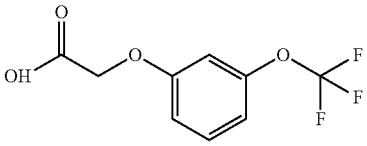
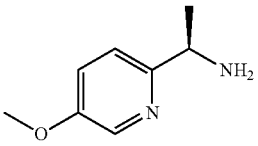
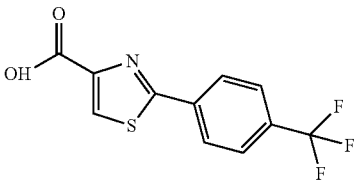
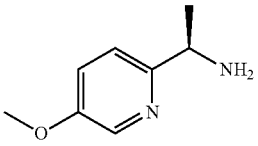
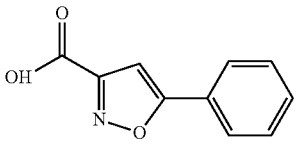
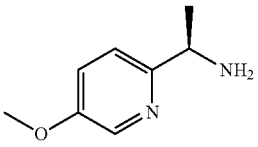
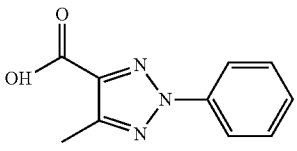
Example 404			401.1	1.74 min	HPLC
Example 405			421.1	1.76 min	HPLC
Example 406			341.3	1.95 min	HPLC
Example 407			353.2	1.72 min	HPLC
Example 408			369.1	1.73 min	HPLC
Example 409			406.1	1.90 min	HPLC
Example 410			324.1	1.71 min	HPLC
Example 411			338.1	1.80 min	HPLC

TABLE 3-continued

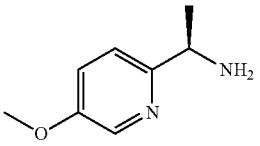
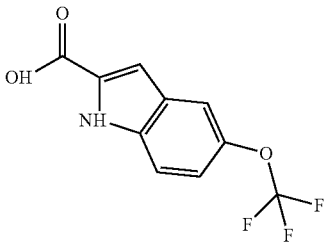
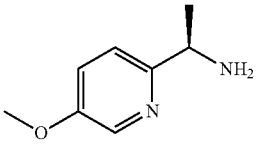
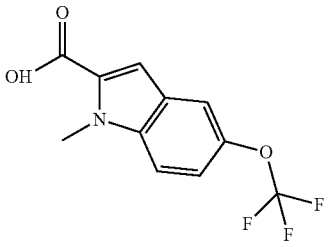
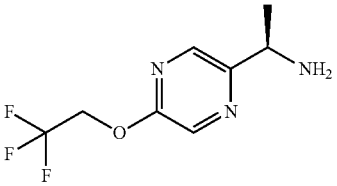
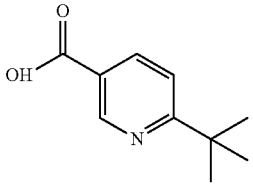
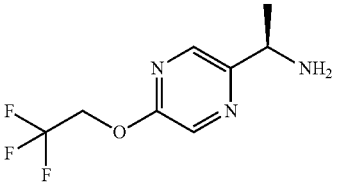
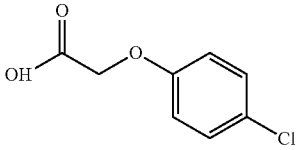
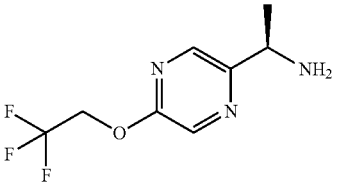
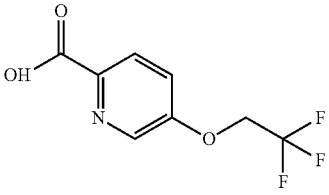
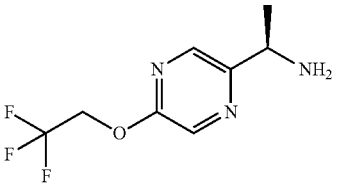
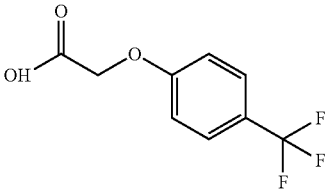
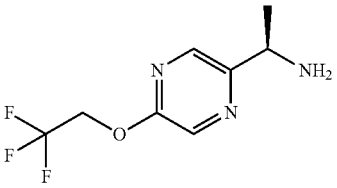
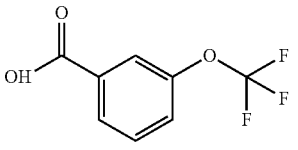
Example 412			378.1	1.73 min	HPLC
Example 413			392.1	1.85 min	HPLC
Example 414			381.1	1.79 min	HPLC
Example 415			388.1	1.83 min	HPLC
Example 416			423.1	1.84 min	HPLC
Example 417			422.1	1.86 min	HPLC
Example 418			408	1.87 min	HPLC

TABLE 3-continued

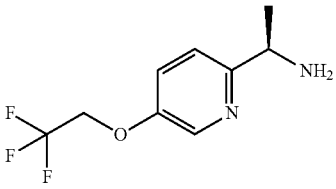
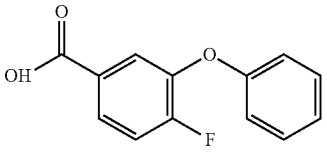
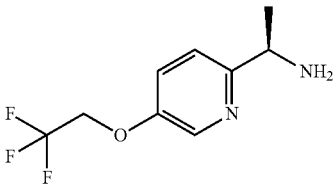
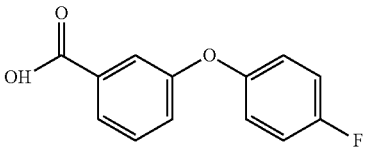
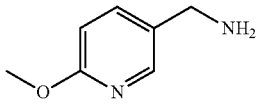
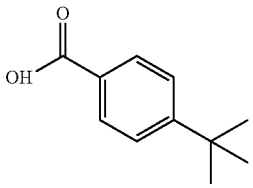
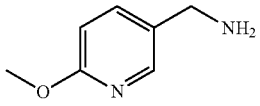
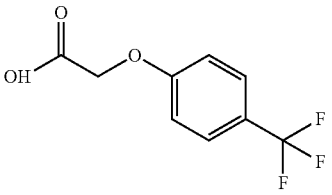
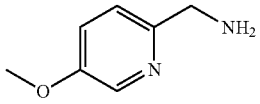
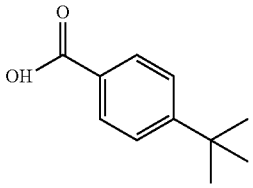
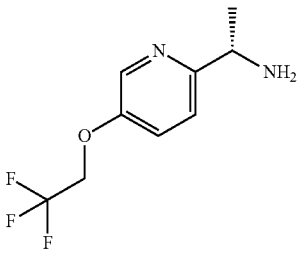
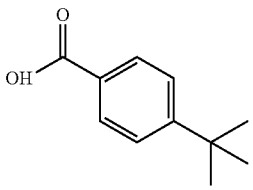
Exemple 419			433.1	1.87 min	HPLC
Exemple 420			433.1	1.87 min	HPLC
Example 421			297.3	1.74 min	HPLC
Example 422			339.1	1.64 min	HPLC
Example 423			297.3	1.68 min	HPLC
Example 424	Alternative route		409.9	1.89 min	HPLC
Example 425	Alternative route		430.9	1.92 min	HPLC
Example 426	Alternative route		430.9	1.91 min	HPLC
Example 427			379.3	1.90 min	HPLC

TABLE 3-continued

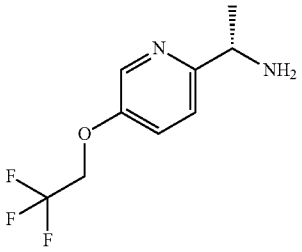
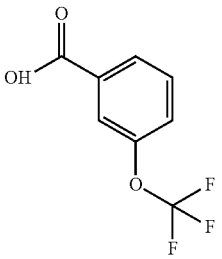
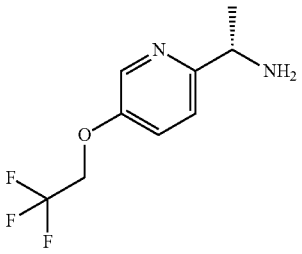
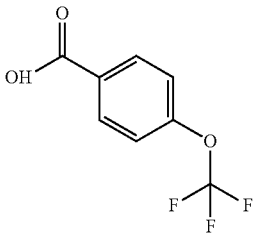
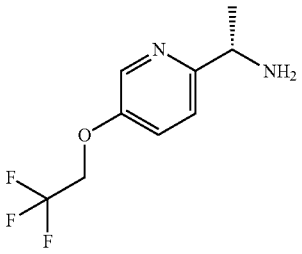
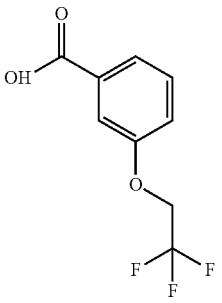
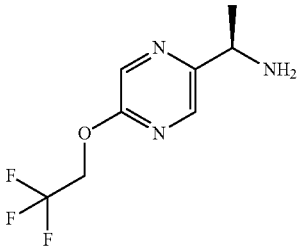
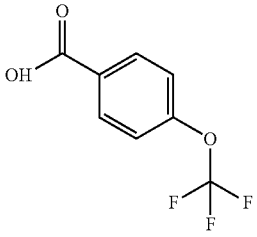
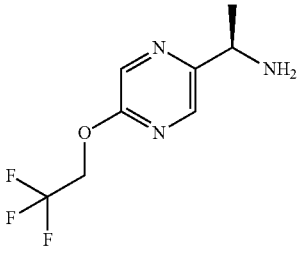
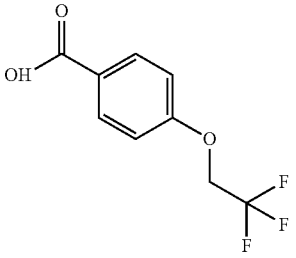
Example 428			407.2	1.81 min	HPLC
Example 429			407.2	1.80 min	HPLC
Example 430			421.2	1.76 min	HPLC
Example 431			408.1	1.86 min	HPLC
Example 432			422.3	1.79 min	HPLC

TABLE 3-continued

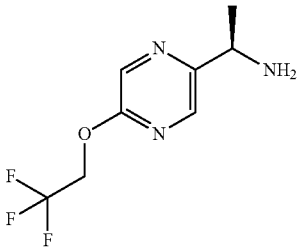
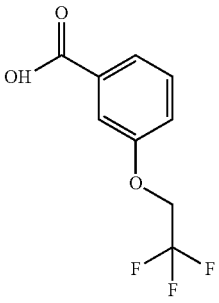
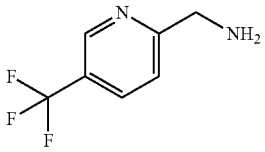
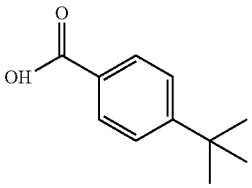
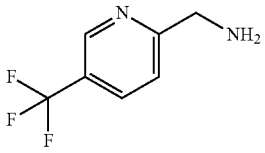
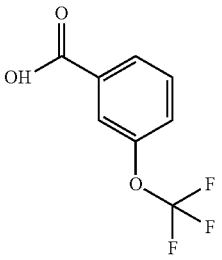
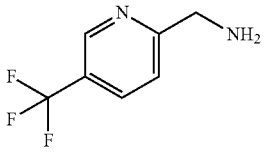
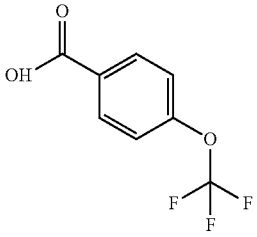
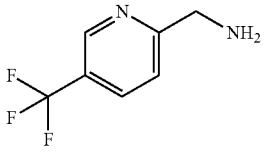
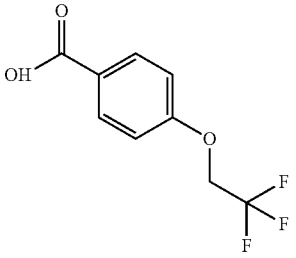
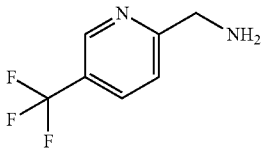
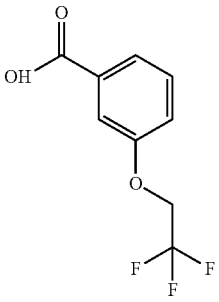
Example 433			422.1	1.82 min	HPLC
Example 434			335.3	1.86 min	HPLC
Example 435			363.1	1.76 min	HPLC
Example 436			363.2	1.75 min	HPLC
Example 437			377.1	1.68 min	HPLC
Example 438			377.2	1.71 min	HPLC

TABLE 3-continued

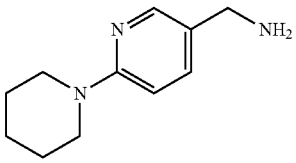
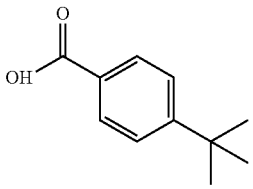
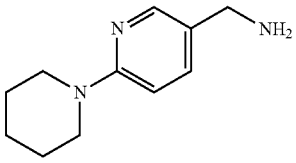
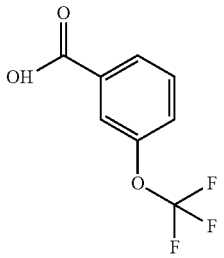
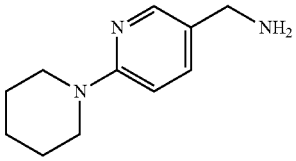
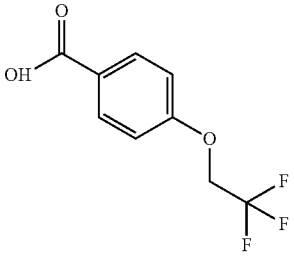
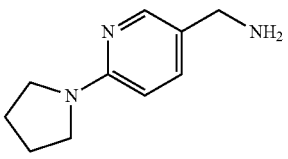
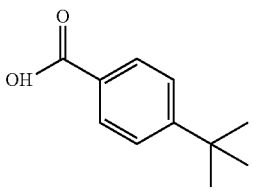
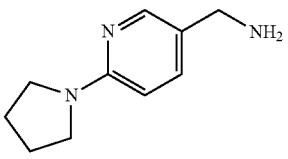
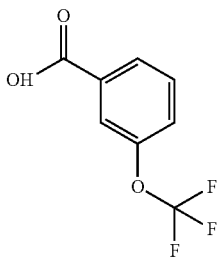
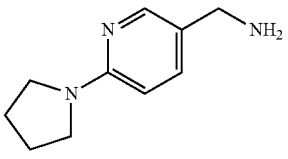
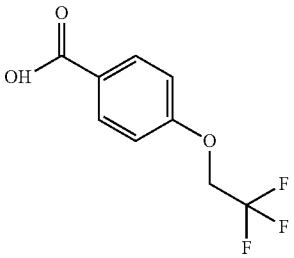
Example 439			350.4	1.95 min	HPLC
Example 440			378.3	1.87 min	HPLC
Example 441			392.3	1.77 min	HPLC
Example 442			336.4	1.81 min	HPLC
Example 443			364.3	1.73 min	HPLC
Example 444			378.3	1.64 min	HPLC

TABLE 3-continued

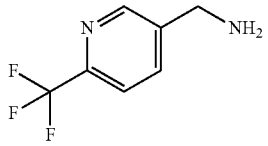
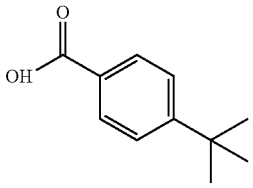
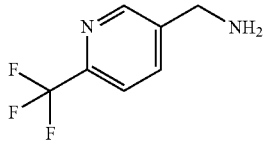
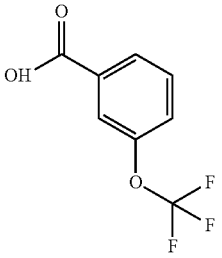
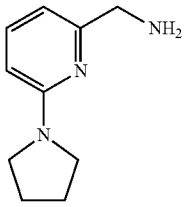
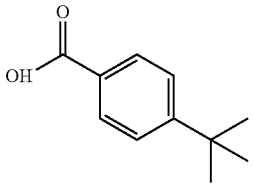
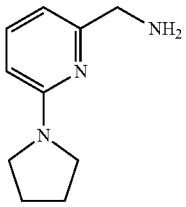
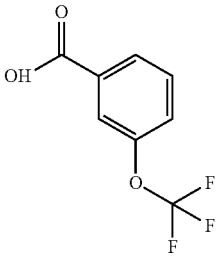
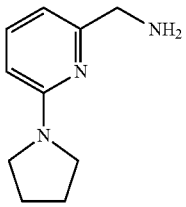
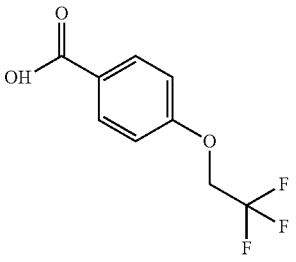
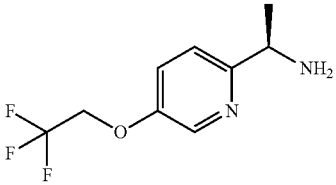
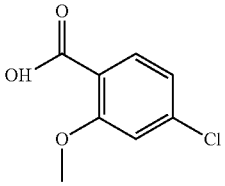
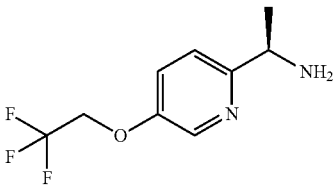
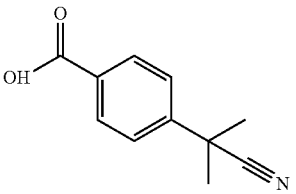
Example 445			335.3	1.84 min	HPLC
Example 446			363.2	1.75 min	HPLC
Example 447			335.3	2.05 min	HPLC
Example 448			363.2	1.95 min	HPLC
Example 449			378.3	1.84 min	HPLC
Example 450			387.2	1.82 min	HPLC
Example 451			390.3	1.67 min	HPLC

TABLE 3-continued

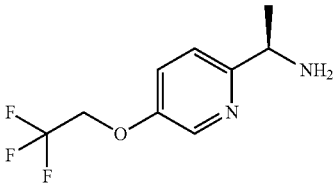
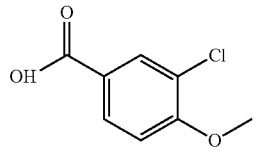
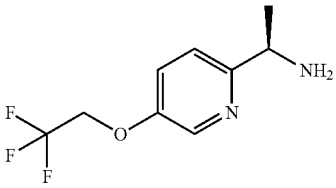
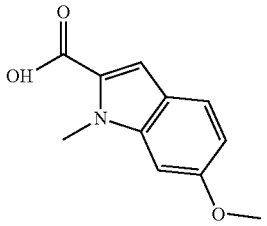
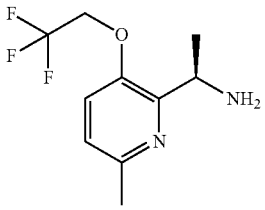
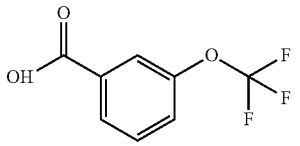
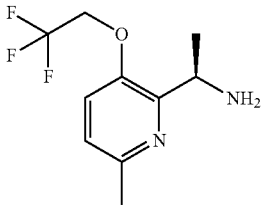
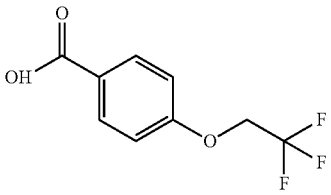
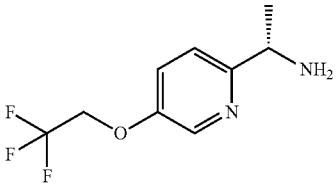
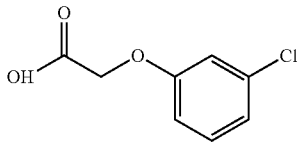
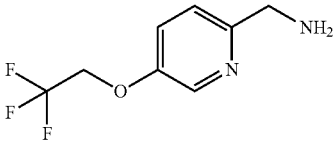
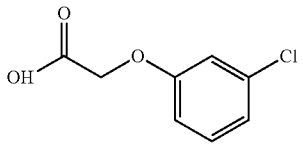
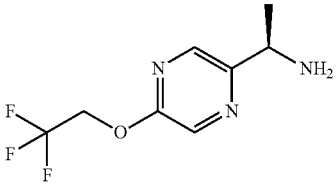
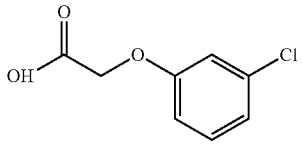
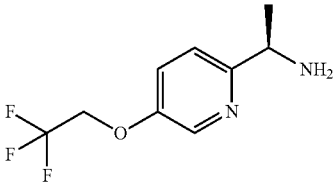
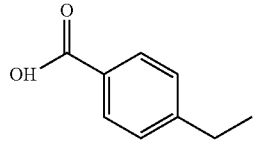
Example 452			387.2	1.70 min	HPLC
Example 453			406.3	1.77 min	HPLC
Example 454			421.2	1.95 min	HPLC
Example 455			435.2	1.86 min	HPLC
Example 456			387.2	1.79 min	HPLC
Example 457			373.2	1.69 min	HPLC
Example 458			388.2	1.84 min	HPLC
Example 459			351	1.75 min	HPLC

TABLE 3-continued

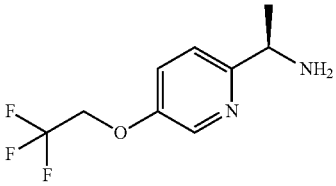
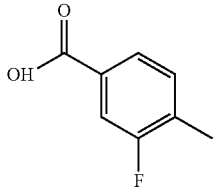
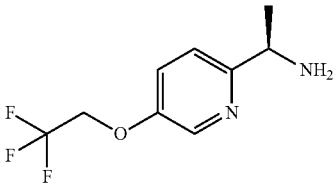
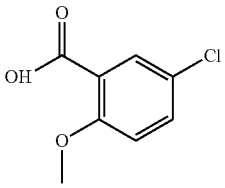
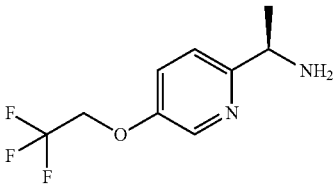
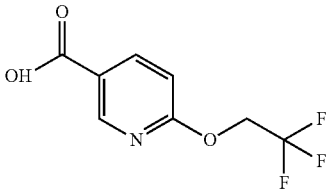
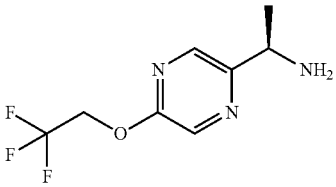
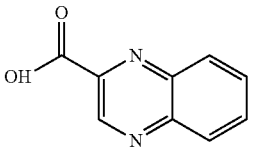
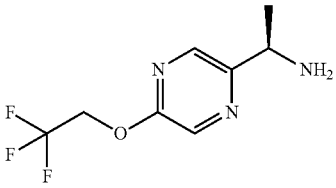
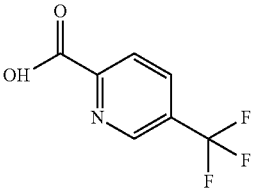
Example 460			357.2	1.71 min	HPLC
Example 461			387.2	1.81 min	HPLC
Example 462			423.9	1.74 min	HPLC
Example 463			376.1	1.78 min	HPLC
Example 464			393.1	1.89 min	HPLC

TABLE 4

Example	spectra data
Example133	^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.85 (1H, s), 8.57 (1H, d, J = 8.0 Hz), 8.36 (1H, d, J = 2.9 Hz), 7.55 (1H, dd, J = 8.8, 2.9 Hz), 7.47 (1H, d, J = 7.3 Hz), 7.37 (1H, d, J = 8.8 Hz), 7.34 (7.3 Hz), 7.15-6.95 (3H, m), 5.04 (1H, m), 4.88 (2H, q, J = 8.8 Hz), 2.23 (1H, m), 1.97 (1H, m), 1.39 (3H, d, J = 6.6 Hz), 1.31 (1H, m), 1.16 (1H, m)
Example134	^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.86 (1H, s), 8.57 (1H, d, J = 8.1 Hz), 8.36 (1H, s), 7.53 (2H, d, J = 7.4 Hz), 7.35 (2H, d, J = 8.1 Hz), 7.15-6.95 (3H, m), 5.04 (1H, m), 4.88 (2H, q, J = 8.8 Hz), 2.31 (1H, m), 1.99 (1H, m), 1.39 (3H, d, J = 6.6 Hz), 1.25 (1H, m), 1.18 (1H, m)
Example203	^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.28 (1H, brs), 8.26 (1H, s), 7.53 (1H, d, J = 8.1 Hz), 7.23-7.13 (4H, m), 6.99 (1H, d, J = 7.3 Hz), 6.82 (1H, dd, J = 8.0, 1.5 Hz) 6.50 (1H, t, J = 2.9 Hz), 5.20 (1H, m), 4.36 (2H, q, J = 8.0 Hz), 2.60 (1H, m), 1.77-1.60 (2H, m), 1.49 (3H, d, J = 6.6 Hz), 1.31 (1H, m)
Example204	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, t, J = 1.4 Hz), 8.20 (1H, brs), 7.56 (1H, d, J = 8.0 Hz), 7.25 (2H, d, J = 2.2 Hz), 7.19 (2H, t, J = 2.2 Hz), 6.94 (1H, d, J = 8.1 Hz), 6.87 (1H, dd, J = 8.0, 1.5 Hz), 6.53 (1H, t, J = 2.2 Hz), 5.20 (1H, m), 4.38 (2H, q, J = 7.3 Hz), 2.64 (1H, m), 1.74 (1H, m), 1.63 (1H, m)., 1.47 (3H, d, J = 7.3 Hz), 1.27 (1H, m).
Example215	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (1H, s), 8.05 (1H, s), 8.03 (1H, d, J = 8.6 Hz), 7.78 (1H, d, J = 6.6 Hz), 7.69 (1H, d, J = 7.9 Hz), 7.44-7.34 (2H, m), 6.62 (1H, brd, J = 7.3 Hz), 5.29 (1H, m), 4.75 (2H, q, J = 7.9 Hz), 2.75 (1H, m), 2.39 (1H, m), 1.84-1.70 (2H, m), 1.52 (3H, d, J = 6.6 Hz),
Example222	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s), 8.10 (1H, s), 8.04 (1H, d, J = 8.0 Hz), 7.92 (1H, d, J = 8.0 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.66 (1H, t, J = 8.0 Hz), 7.46 (1H, t, J = 8.0 Hz), 7.38 (1H, d, J = 8.0 Hz), 6.59 (1H, d, J = 7.3 Hz), 5.27 (1H, quintet, J = 7.3 Hz), 4.81-4.72 (2H, m), 2.82-2.74 (1H, m), 2.37-2.30 (1H, m), 1.68-1.60 (2H, m). 1.47 (3H. d. J = 7.3 Hz).
Example223	^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.0 (1H, s), 8.68 (1H, d, J = 7.7 Hz), 8.11 (1H, d, J = 2.2 Hz), 7.73 (1H, dd, J = 8.4, 2.2 Hz), 7.36 (1H, d, J = 7.3 Hz), 7.23 (1H, d, J =7.7 Hz), 7.00-6.88 (3H, m), 6.12 (1H, s), 5.00-4.91 (3H, m), 2.34 (1H, m), 1.93 (1H, m), 1.37-1.27 (2H, m), 1.35 (3H, d, J = 7.0 Hz).
Example224	^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.0 (1H, s), 8.65 (1H, d,

TABLE 4-continued

Example	spectra data
	J = 8.1 Hz), 8.11 (1H, d, J = 2.2 Hz), 7.74 (1H, dd, J = 8.4, 2.2 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.21 (1H, d, J = 7.7 Hz), 6.99-6.86 (3H, m), 6.09 (1H, s), 4.99-4.90 (3H, m), 2.28 (1H, m). 1.93 (1H, m), 1.74 (1H, m), 1.36 (3H, d, J =7.3 Hz), 1.31 (1H, m).
Example225	^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.0 (1H, s), 8.73 (1H, d, J = 7.3 Hz), 8.43 (1H, d, J = 1.1 Hz), 8.18 (1H, d, J = 1.1 Hz), 7.36 (1H, d, J = 7.7 Hz), 7.23 (1H, d, J = 7.7 Hz), 7.00-6.88 (2H, m), 6.12 (1H, s), 5.06-4.97 (3H, m), 2.34 (1H, m), 2.01 (1H, m), 1.39 (3H, d, J = 7.0 Hz), 1.30-1.26 (2H, m).
Example226	^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.0 (1H, s), 8.72 (1H, d, J = 7.7 Hz), 8.42 (1H, d, J = 1.1 Hz), 8.20 (1H, d, J = 1.1 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.21 (1H, d, J = 8.1 Hz), 6.99-6.87 (2H, m), 6.09 (1H, s), 5.06-4.97 (3H, m), 2.29 (1H, m), 2.01 (1H, m), 1.39 (3H, d, J = 7.0 Hz), 1.37-1.29 (2H, m).
Example227	^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.60 (1H, d, J = 7.7 Hz), 8.31 (1H, d, J = 2.9 Hz), 7.94 (1H, s), 7.62 (1H, d, J = 8.4 Hz), 7.49 (1H, dd, J = 8.4, 2.9 Hz), 7.40 (1H, s), 7.30 (1H, d, J = 8.8 Hz), 6.87 (1H, d, J = 8.4 Hz), 4.97 (1H, quintet, J = 7.3 Hz), 4.83 (2H, q, J = 8.8 Hz), 3.98 (3H, s), 2.39 (1H, m), 2.07 (1H, m), 1.33 (3H, d, J = 7.3 Hz), 1.35-1.28 (2H. m).
Example237	^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.55 (1H, d, J = 7.7 Hz), 8.30 (1H, d, J = 2.9 Hz), 7.48 (1H, dd, J = 8.8, 2.9 Hz), 7.42-7.27 (6H, m), 7.02 (2H, d, J = 8.8 Hz), 6.89 (2H, d, J = 8.4 Hz), 5.05 (2H, s), 4.95 (1H, quintet, J = 7.3 Hz), 4.83 (2H, q, J = 8.8 Hz), 2.17 (1H, m), 1.88 (1H, m), 1.32 (3H, d, J = 7.3 Hz), 1.21 (1H, m), 1.08 (1H, m).
Example238	^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.54 (1H, d, J = 8.1 Hz), 8.28 (1H, d, J = 2.9 Hz), 7.47 (1H, dd, J = 8.8, 2.9 Hz), 7.41-7.26 (6H, m), 6.99 (2H, d, J = 8.8 Hz), 6.88 (2H, d, J = 8.4 Hz), 5.04 (2H, s), 4.95 (1H, quintet, J = 7.3 Hz), 4.81 (2H, q, J = 8.8 Hz), 2.11 (1H, m), 1.90 (1H, m), 1.33 (3H, d, J = 7.3 Hz), 1.27 (1H, m), 1.09 (1H, m).
Example240	^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.57 (1H, d, J = 7.7 Hz), 8.30 (1H, d, J = 2.9 Hz), 7.50-7.27 (7H, m), 7.16 (1H, t, J = 7.7 Hz), 6.81-6.76 (2H, m), 6.68 (1H, d, J = 7.3 Hz), 5.06 (2H, s), 4.95 (1H, quintet, J = 7.0 Hz), 4.83 (2H, q, J = 8.8 Hz), 2.19 (1H, m), 1.99 (1H, m), 1.32 (3H, d, J = 7.0 Hz), 1.25 (1H, m), 1.15 (1H, m).
Example241	^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.56 (1H, d, J = 8.1 Hz), 8.28 (1H, d, J = 2.9 Hz), 7.49-7.27 (7H, m), 7.15 (1H, t, J = 7.7 Hz), 6.81-6.64 (3H, m), 5.04 (2H, s), 4.96 (1H, quintet, J = 7.0 Hz), 4.81 (2H, q, J = 8.8 Hz), 2.14 (1H, m), 2.01 (1H, m), 1.33 (3H, d, J = 7.0 Hz), 1.32 (1H, m), 1.16 (1H, m).
Example246	^{1}H-NMR(300 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.31-7.21 (2H, m), 7.13 (1H, dd, J = 8.8, 2.9 Hz), 7.08-6.85 (3H, m), 5.19 (1H, m), 4.40 (2H, q, J = 8.1 Hz), 2.65 (1H, m), 1.63-1.51 (2H, m), 1.48 (3H, d, J = 6.6 Hz), 1.21 (1H, m)
Example247	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s), 7.26 (2H, m), 7.08 (1H, dd, J = 7.1, 2.2 Hz), 7.00 (1H, m), 6.96-6.83 (2H, m), 5.19 (1H, m), 4.40 (2H, q, J = 7.3 Hz), 2.58 (1H, m), 1.65 (1H, m), 1.54 (1H, m), 1.47 (3H, d, J = 6.6 Hz), 1.23 (1H, m)
Example248	^{1}H-NMR (300 Mhz, $CDCl_3$) δ 8.29 (1H, s), 7.24 (2H, d, J = 2.2 Hz), 6.90 (2H, t, J = 8.1 Hz), 6.63-6.57 (2H, m), 5.17 (1H, m), 4.39 (2H, q, J = 8.0 Hz), 3.78 (3H, s), 2.55 (1H, m), 1.67 (1H, m), 1.53 (1H, m), 1.47 (3H, d, J = 6.6 Hz), 1.19 (1H, m)
Example249	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.24 (2H, d, J = 1.5 Hz), 6.95-6.80 (2H, m) 6.64-6.51 (2H, m), 5.17 (1H, m), 4.39 (2H, d, J = 8.0 Hz), 3.76 (3H, s), 2.50 (1H, m), 1.67 (1H, m), 1.58 (1H, m), 1.46 (3H, d, J = 6.6 Hz), 1.23 (1, m)
Example250	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s), 7.25 (2H, d, J = 6.6 Hz), 6.94 (1H, brd, J = 7.3 Hz), 6.65-6.55 (2H, m), 5.18 (1H, m), 4.40 (2H, q, J = 8.0 Hz), 2.39 (1H, m), 1.93 (1H, m), 1.55 (1H, m), 1.48 (3H, d, J = 6.6 Hz), 1.32 (1H, m)
Example251	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.25 (2H, m), 7.18 (1H, t, J = 7.3 Hz), 7.02 (1H, d, J = 7.3 Hz), 6.96-6.85(3H, m), 5.16 (1H, m), 4.39 (2H, q, J = 8.0 Hz), 2.45 (1H, m), 2.33 (3H, s), 1.68 (1H, m), 1.58 (1H, m), 1.45 (3H d J = 6.6 Hz). 1.21 (1H. m)
Example252	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26 (1H, s), 7.26-7.29 (2H, m), 7.15 (1H, t, J = 7.3 Hz), 6.99 (1H, d, J = 7.4 Hz), 6.94-6.84(3H, m,), 5.16 (1H, m), 4.38 (2H, q, J = 8.1 Hz), 2.41 (1H, m), 2.30 (3H, s), 1.71-1.59 (2H, m), 1.46 (3H, d, J = 6.6 Hz), 1.26 (1H, m)
Example253	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, d, J = 1.5 Hz), 7.28-7.20 (2H, m), 6.99 (1H, brd, J = 8.4 Hz), 6.70-6.55 (3H, m), 5.15 (1H, m), 4.40 (2H, q, J = 8.1 Hz), 2.49 (1H, m), 1.70 (1H, m), 1.62 (1H, m), 1.46 (3H, d, J = 6.6 Hz), 1.18 (1H, m)
Example254	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (1H, d, J = 1.5 Hz), 7.26-7.20 (2H, m), 6.96 (1H, brd, J = 7.3 Hz), 6.67-6.53 (3H, m), 5.15 (1H, m), 4.39 (2H, q, J = 8.1 Hz), 2.44 (1H, m), 1.74-1.62 (2H, m), 1.46 (3H, d, J = 6.6 Hz), 1.22 (1H. m)
Example260	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.57-7.50 (2H, m), 7.30-7.20 (4H, m), 5.16 (1H, quintet, J = 6.6 Hz), 4.39 (2H, q, J = 8.1 Hz), 2.75-2.68 (1H, m), 2.45-2.37 (1H, m), 1.75-1.65 (2H, m), 1.44 (3H, d, J = 6.6 Hz). (signals due to two NH were not observed)
Example261	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, s), 7.41 (2H, s), 7.31-7.25 (2H, m), 7.19-7.13 (2H, m), 7.05 (1H, m), 5.29 (1H, m), 3.97 (2H, d, J = 6.6 Hz), 2.79 (1H, m), 1.72 (1H, m), 1.61 (3H, d, J = 6.6 Hz), 1.42 (1H, m), 1.33 (1H, m), 0.81 (2H, m), 0.51 (2H, m)
Example262	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, s), 7.32 (2H, d, J = 2.2 Hz), 7.22 (1H, dd, J = 8.8, 2.9 Hz), 7.17-7.10 (2H, m), 7.03 (1H, m), 5.30 (IH, m), 3.98 (2H, d, J = 6.6 Hz), 2.73 (1H, m), 1.77 (1H, m), 1.60 (3H, d, J = 6.6 Hz), 1.50-1.30 (2H, m), 0.82 (2H, m), 0.52 (2H, m)
Example263	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, s), 7.30 (2H, s), 7.10-7.00 (2H, m), 6.80-6.70 (2H, m), 5.27 (1H, m), 3.97 (2H, d, J = 6.6 Hz), 3.92 (3H, s), 2.69 (1H, m), 1.81 (1H, m), 1.65 (1H, m), 1.60 (3H, d, J = 6.6 Hz), 1.42 (1H, m), 1.32 (1H, m), 0.81 (2H, m), 0.51 (1H, m)
Example264	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, s), 7.30 (2H, s), 7.10-6.98 (2H, m), 6.75-6.65 (2H, m), 5.28 (1H, m), 3.97 (2H, d, J = 7.3 Hz), 3.90 (3H, s), 2.65 (1H, m), 1.82 (1H, m), 1.75 (1H, m), 1.59 (3H, d, J = 6.6 Hz), 1.45-1.30 (2H, m), 0.82 (2H, m), 0.51 (2H, m)
Example265	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, s), 7.31 (2H, d, J = 1.5 Hz), 7.16 (1H, brd, J = 7.3 Hz), 6.80-6.65 (2H, m), 5.28 (1H, m), 3.98 (2H, d, J = 7.4 Hz), 2.50 (1H, m), 2.10 (1H, m), 1.77-1.60 (2H, m), 1.60 (3H, d, J = 7.3 Hz), 1.53 (1H, m), 1.42 (1H, m), 0.81 (2H, m), 0.52 (2H, m)
Example266	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, s), 7.31 (1H, d, J = 1.5 Hz), 7.15 (1H, brd, J = 7.3 Hz), 6.80-6.70 (2H, m), 5.28 (1H, m), 3.98 (2H, d, J = 7.3 Hz), 2.53 (1H, m), 2.07 (1H, m), 1.68 (1H, m), 1.61 (3H, d, J = 6.6 Hz), 1.50-1.40 (2H, m), 0.80 (2H, m), 0.51 (2H, m)
Example267	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.37 (1H, s), 7.35-7.28 (3H, m), 7.15 (1H, d, J = 8.0 Hz), 7.10-7.00 (2H, m), 5.26 (1 H, m), 3.97 (2H, d, J = 7.3 Hz), 2.61 (1H, m), 2.47 (3H, s), 1.83 (1H, m), 1.73 (1H, m), 1.58 (3H, d, J = 6.6 Hz), 1.42 (1H, m), 1.33 (1H, m), 0.82 (2H, m), 0.51 (2H, m)
Example268	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, s), 8.12 (1H, d, J = 1.5 Hz), 7.16 (1H, dd, J = 8.1, 2.2 Hz), 7.05 (1H, dd, J = 8.8, 5.9 Hz), 6.94 (1H, m), 6.57 (1H, brd, J = 8.1 Hz), 5.31 (1H, m), 4.79 (2H, q, J = 8.1 Hz), 2.65 (1H, m), 1.65-1.49 (2H, m), 1.53 (3H, d, J = 6.6 Hz), 1.23 (1H, m)
Example269	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, s), 8.14 (1H, s), 7.11 (1H, dd, J = 8.1, 2.2 Hz), 7.03 (1H, dd, J = 8.1, 6.6 Hz), 6.90 (1H, m), 6.57 (1H, brd, J = 8.0 Hz), 5.30 (1H, m), 4.85-4.70 (2H, m), 2.57 (1H, m), 1.68 (1H, m), 1.52 (3H, d, J = 7.3 Hz), 1.52 (1H, m), 1.27 (1H, m)
Example270	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, s), 8.12 (1H, s), 6.93 (1H, t, J = 8.0 Hz), 6.66-6.60 (2H, m), 6.51 (1H, brd, J = 8.1 Hz), 5.29 (1H, m), 4.79 (2H, q, J = 8.8 Hz), 3.81 (3H, s), 2.57 (1H, m), 1.67 (1H, m), 1.54 (1H, m), 1.52 (3H, d, J = 6.6 Hz), 1.23 (1H, m)
Example271	^{1}H-NMR(300 MHz, CDl_3) δ 8.34 (1H, s), 8.12 (1H, s), 6.70-6.55 (3H, m), 5.29 (1H, m), 4.83-4.73 (2H, m), 2.42

TABLE 4-continued

Example	spectra data
	(1H, m), 1.89 (1H, m), 1.58 (1H, m), 1.54 (3H, d, J = 6.6 Hz), 1.35 (1H, m)
Example272	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.34 (1H, s), 8.12 (1H, s), 6.67-6.55 (3H, m), 5.29 (1H, m), 4.83-4.73 (2H, m), 2.35 (1H, m), 1.90 (1H, m), 1.61 (1H, m), 1.53 (3H, d, J = 7.3 Hz), 1.40 (1H, m)
Example273	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, s), 8.11 (1H, d, J = 1.5 Hz), 7.21 (1H, t, J = 7.4 (1H, m), 7.04 (1H, d, J = 7.3 Hz), 6.94 (1H, s), 6.92 (1H, d, J = 8.8 Hz), 6.50 (1H, brd, J = 8.1 Hz), 5.28 (1H, m), 4.79 (2H, q, J = 7.3 Hz), 2.50 (1H, m), 2.36 (3H, s), 1.70-1.55 (2H, m), 1.50 (3H, d, J = 7.3 Hz)1.23 (1H, m)
Example274	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s), 8.10 (1H, s), 7.17 (1H, t, J = 7.3 Hz), 7.02 (1H, d, J = 8.0 Hz), 6.89 (1H, s), 6.88 (1H, d, J = 7.3 Hz), 6.52 (1H, brd, J = 8.0 Hz), 5.28 (1H, m), 4.83-4.70 (2H, m), 2.43 (1H, m), 2.33 (3H, s), 1.69-1.55 (2H, m), 1.51 (3H, d, J = 6.6 Hz), 1.29 (1H, m)
Example275	^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.58 (1H, brs), 8.29 (1H, s), 7.54 (1H, d, J = 8.0 Hz), 7.29-7.26 (3H, m), 7.04 (1H, t, J = 8.0 Hz), 6.89 (1H, d, J = 6.6 Hz), 6.71 (1H, d, J = 8.0 Hz), 6.59 (1H, s), 5.19 (1H, m), 4.38 (2H, q, J = 8.0 Hz), 2.53 (1H, m), 1.75-1.65 (2H, m), 1.49 (3H, d, J = 6.6 Hz), 1.42 (1H, m).
Example276	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.75 (1H, brs), 8.29 (1H, s), 7.53 (1H, d, J = 8.1 Hz), 7.30-7.20 (3H, m), 7.07-6.90 (2H, m), 6.85 (1H, d, J = 7.3 Hz), 6.58 (1H, s), 5.18 (1H, m), 4.39 (2H, q, J = 8.1 Hz), 2.72 (1H, m), 1.78 (1H, m), 1.58 (1H, m). 1.49 (3H, d, J = 6.6 Hz), 1.35 (1H, m)
Example277	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, s), 1.25 (1H, brs), 7.29-7.23 (4H, m), 7.13 (1H, t, J = 8.0 Hz), 6.89 (1H, d, J = 7.3 Hz), 6.77-6.72 (2H, m), 5.21 (1H, m), 4.39 (2H, q, J = 7.3 Hz), 2.85 (1H, m), 1.83 (1H, m), 1.66 (1H, m), 1.48 (3H, d, J = 6.6 Hz). 1.38 (1H, m)
Example278	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, d, J = 1.4 Hz), 8.22 (1H, brs), 8.10 (1H, d, J = 1.5 Hz), 7.25 (1H, m), 7.20 (1H, m), 7.10 (1H, t, J = 7.4 Hz), 6.71 (1H, d, J = 7.3 Hz), 6.60 (1H, d, J = 2.9 Hz), 6.51 (1H, brd, J = 8.1 Hz), 5.29 (1H, m), 4.81-4.70 (2H, m), 2.78 (1H, m), 1.79 (1H, m), 1.73 (1H, m), 1.50 (3H, d, J = 7.3 Hz), 1.44 (1H, m)
Example279	^{1}H-NMR (300 MHz,$CDCl_3$) δ 8.30 (1H, d, J = 1.5 Hz), 8.25 (1H, brs), 8.11 (1H, s), 7.29-7.25 (2H, m), 7.13 (1H, t, J = 7.3 Hz), 6.75-6.70 (2H, m), 6.50 (1H, brd, J = 7.3 Hz), 5.30 (1H, m), 4.80-4.70 (2H, m), 2.86 (1H, m), 1.77 (1H. m). 1.64 (1H. m). 1.50 (3H. d. J = 6.6 Hz). 1.39 (1H, m)
Example280	^{1}H-NMR(300 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.32-7.10 (7H, m), 6.88 (1H, brs), 5.15 (1H, m), 4.40 (2H, q, J = 8.0 Hz), 2.53 (1H, m), 1.70 (1H, m), 1.660 (1H, m), 1.46 (3H, d, J = 6.6 Hz), 1.21 (1H, m)
Example281	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26 (1H, d, J = 1.5 Hz), 7.29-7.14 (5H, m), 7.06 (2H, d, J = 6.6 Hz), 6.89 (1H, brd, J =8.0 Hz), 5.16 (1H, m), 4.38 (2H, q, J = 8.0 Hz), 2.45 (1H, m), 1.73-1.60 (2H, m), 1.46 (3H, d, J = 6.6 Hz), 1.25 (1H, m)
Example282	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, d, J = 1.5 Hz), 8.09 (1H, s), 7.35-7.17 (3H, m), 7.10 (2H, d, J = 6.6 Hz), 6.48(1H, brd, J = 7.3 Hz), 5.27 (1H, m), 4.75 (2H, q, J = 7.3 Hz), 2.50 (1H, m), 1.67-1.54 (2H, m), 1.47 (3H, d, J= 6.6 Hz), 1.21 (1H, m)
Example283	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (1H, d, J = 1.5 Hz), 8.07 (1H, d, J = 1.5 Hz), 7.28-2.14 (3H, m), 7.05 (2H, d, J = 7.5 Hz), 6.50 (1H, brd, J = 7.3 Hz), 5.25 (1H, m), 4.81-4.68 (2H, m), 2.45 (1H, m), 1.67-1.62 (2H, m), 1.48 (3H, d, J = 6.6 Hz), 1.26 (1H, m)
Example284	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, d, J = 2.2 Hz), 7.61 (1H, dd, J = 8.8, 2.9 Hz), 7.31-7.18 (3H, m), 7.08 (2H, d, J = 6.6 Hz), 6.85 (1H, d, J = 8.1 Hz), 5.81 (1H, brd, J = 7.3 Hz), 5.13 (1H, m), 4.75 (2H, q, J = 8.8 Hz), 2.49 (1H, m), 1.65-1.55 (2H, m), 1.50 (2H, d, J = 6.6 Hz), 1.23 (1H, m)
Example285	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, d, J = 2.2 Hz), 7.61 (1H, m), 7.29-7.06 (3H, m), 7.05 (2H, d, J = 6.6 Hz), 8.83(1H, d, J = 8.8 Hz), 5.80 (1H, brd, J = 7.3 Hz), 5.13 (1H, m), 4.73 (2H, q, J = 8.8 Hz), 2.46 (1H, m), 1.67-1.55 (2H, m), 1.51 (3H, d, J = 6.6 Hz), 1.25 (1H, m)

TABLE 4-continued

Example	spectra data
Example286	^{1}H-NMR(300 MHz, $CDCl_3$) δ 11.67 (1H, brs), 8.29 (1H, s), 8.11 (1H, s), 7.68-7.30 (3H, m), 7.23-7.12 (2H, m), 5.20 (1H, m), 4.77 (2H, q, J = 8.8 Hz), 2.60 (1H, m), 2.37 (1H, m), 1.66-1.56 (2H, m), 1.48 (3H, d, J = 6.6 Hz)
Example287	^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.78 (1H, s), 8.13 (1H, s), 7.91 (1H, m), 7.68 (1H, d, J = 8.8 Hz), 7.55 (1H, m), 7.40 (1H, m), 7.23-7.08 (2H, m), 6.83 (1H, m), 5.08 (1H, m), 4.84-4.67 (2H, m), 2.60 (1H, m), 2.37 (1H, m), 1.61 (2H, m), 1.46 (3H, d, J = 6.6 Hz)
Example288	^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.66 (1H, brs), 8.10 (1H, d, J = 2.2 Hz), 7.71 (1H, d, J = 7.3 Hz), 7.64 (1H, dd, J = 8.0, 2.2 Hz), 7.47 (1H, m), 7.37 (1H, m), 7.21-7.11 (2H, m), 6.79 (1H, d, J = 8.1 Hz), 5.07 (1H, m), 4.74 (2H, q, J=8.8 Hz), 2.56 (1H, m), 2.32 (1H, m), 1.70-1.60 (2H, m), 1.48 (3H, d, J = 6.6 Hz)
Example289	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13 (1H, d, J = 2.9 Hz), 7.61 (1H, dd, J = 2.2 & 8.8 Hz), 7.45-7.35 (1H, m), 7.20-7.13 (1H, m), 6.97 (1H, dt, J = 2.2 & 8.8 Hz), 6.87 (1H, d, J = 8.8 Hz), 6.23 (1H, d, J = 7.3 Hz), 5.10 (1H, quintet, J = 7.3 Hz), 4.76 (2H, q, J = 8.8 Hz), 2.70-2.60 (1H, m), 2.36-2.29 (1H, m), 1.70-1.58 (2H, m), 1.50 (3H, d, J = 7.3 Hz) (a signal due to NH was not observed)
Example290	^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (1H, d, J = 2.2 Hz), 7.46 (1H, dd, J = 2.2 & 8.8 Hz), 7.40-7.34 (1H, m), 7.17-7.10 (1H, m), 6.94 (1H, dt, J = 2.2 & 8.8 Hz), 6.70 (1H, d, J = 7.4 Hz), 6.62 (1H, d, J = 8.8 Hz), 5.05 (1H, quintet, J =7.3 Hz), 4.62 (2H, q, J = 7.3 Hz), 2.62-2.53 (1H, m), 2.30-2.23 (1H, m), 1.77-1.69 (2H, m), 1.51 (3H, d, J = 7.3 Hz) (a signal due to NH was not observed)
Example291	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, d, J = 2.9 Hz), 7.90-7.80 (1H, m), 7.63-7.50 (1H, m), 7.50-7.44 (2H, m), 7.32-7.24(1H, m), 5.16 (1H, quintet, J = 7.3 Hz), 4.42 (2H, q, J = 8.1 Hz), 2.82-2.76 (1H, m), 2.52-2.45 (1H, m), 1.75-1.68 (2H, m), 1.45 (3H, d, J = 7.3 Hz) (a signal due to NH was not observed)
Example292	^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.74 (1H, s), 8.60 (1H, d, J = 8.1 Hz), 8.04 (1H, d, J = 2.9 Hz), 7.81 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.1 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.10 (1H, dd, J = 8.4, 2.9 Hz), 5.11 (1H, quintet, J = 7.0 Hz), 1.43 (3H, d, J = 7.0 Hz), 1.28 (9H, s), LCMS (Method A) m/z: M + 1 obs 299.2, tR = 3.21 min.
Example307	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, s), 7.16 (2H, d, J = 1.4 Hz), 6.96-7.84 (3H, m), 6,74 (1H, d, J = 7.7 Hz), 5.12 (1H, m), 3.83 (2H, d, J = 7.3 Hz), 3.81 (3H, s), 2.44 (1H, m), 2.20 (3H, s), 1.62 (1H, m), 1.53 (1H, m), 1.44 (3H, d, J = 6.6 Hz), 1.28 (1H, m), 1.14 (1H, m), 0.67 (2H, m), 0.37 (2H, m)
Example308	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21 (1H, s), 7.15 (2H, s), 6.98-6.79 (3H, m), 6.71 (1H, d, J = 8.1 Hz), 5.12 (1H, m), 3.82 (2H, d, J = 7.3 Hz), 3.79 (3H, s), 2.38 (1H, m), 2.17 (3H, s), 1.66-1.53 (2H, m), 1.44 (3H, d, J = 6.6 Hz), 1.27 (1H, m), 1.19 (1H, m), 0.67 (2H, m), 0.36 (2H, m)
Example309	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s), 8.09 (1H, s), 6.92 (1H, d, J = 7.9 Hz), 6.87 (1H, s), 6.74 (1H, d, J = 7.9 Hz), 6.44 (1H, brd, J = 7.3 Hz), 5.25 (1H, m), 4.76 (2H, q, J = 8.8 Hz), 3.81 (3H, s), 2.44 (1H, m), 2.20 (3H, s), 1.58-1.50 (2H, m), 1.47 (3H, d, J = 6.6 Hz), 1.16 (1H, m)
Example310	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, s), 8.08 (1H, s), 6.87 (1H, d, J = 8.1 Hz), 6.82 (1H, s), 6.71 (1H, d, J = 8.1 Hz), 6.47 (1H, brd, J = 7.3 Hz), 5.26 (1H, m), 4.81-4.69 (2H, m), 3.79 (3H, s), 2.38 (1H, m), 2.17 (3H, s), 1.62-1.53 (2H, m), 1.48 (3H, d, J = 6.6 Hz), 1.21 (1H, m)
Example316	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.79 (1H, brs), 8.24 (1H, s), 7.54 (1H, d, J = 8.0 Hz), 7.178 (2H, d, J = 1.4 Hz), 7.08-7.02 (2H, m), 6.85 (1H, d, J = 6.6 Hz), 6.58 (1H, m), 5.14 (1H, m), 3.84 (2H, d, J = 7.4 Hz), 2.72 (1H, m), 1.79 (1H, m), 1.59 (1H, m), 1.49 (3H, d, J = 6.6 Hz), 1.36 (1H, m), 1.28 (1H, m), 0.68 (2H, m), 0.37 (2H, m)
Example317	^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.77 (1H, brs), 8.24 (1H, s), 7.54 (1H, d, J = 8.0 Hz), 7.26 (1H, m), 7.21 (2H, d, J = 1.4 Hz), 7.04 (1H, t, J = 7.3 Hz), 6.89 (1H, d, J = 6.6 Hz), 6.71 (1H, brd, J = 8.1 Hz), 6.59 (1H, m), 5.17 (1H, m), 3.82 (2H, d, J = 6.6 Hz), 2.52 (1H, m), 1.73-1.62 (2H, m),

TABLE 4-continued

Example	spectra data
	1.48 (3H, d, J = 6.6 Hz), 1.45 (1H, m), 1.27 (1H, m), 0.66 (2H, m), 0.35 (2H, m)
Example318	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, s), 8.08 (1H, s), 7.31-7.26 (2H,, m), 6.96 (1H, t, J = 7.4 Hz), 6.89 (2H, t, J = 8.3 Hz), 6.47 (1H, d, J = 7.3 Hz), 5.23 (1H, m), 4.75 (2H, q, J = 8.8 Hz), 4.04 (1H, dd, J = 10.3, 2.9 Hz), 3.84 (1H, dd, J = 10.3, 6.6 Hz), 1.89 (1H, m), 1.52 (1H, m), 1.49 (3H, d, J = 6.6 Hz), 1.24 (1H, m), 0.89 (1H, m)
Example319	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, s), 8.08 (1H, s), 7.28-7.23 (2H, m), 6.94 (1H, t, J = 6.6 Hz), 6.84 (2H, d, J = 8.8 Hz), 6.50 (1H, d, J = 7.4 Hz), 5.23 (1H, m), 4.77 (2H, q, J = 8.0 Hz), 3.99 (1H, dd, J = 10.3, 5.9 Hz), 3.82 (1H, dd, J = 10.3, 6.6 Hz), 1.84 (1H, m), 1.52 (1H, m), 1.48 (3H, d, J = 6.6 Hz), 1.31 (1H, m), 0.93 (1H, m)
Example320	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, d, J = 2.9 Hz), 7.61 (1H, dd, J = 8.8, 2.9 Hz), 7.31-7.26 (2H, m), 6.96 (1H, t, J = 7.3 Hz), 6.90-6.82 (3H, m), 5.82 (1H, brd, J = 7.3 Hz), 5.11 (1H, m), 4.75 (2H, q, J = 8.8 Hz), 4.08 (1H, dd, J = 10.3, 5.1 Hz,), 3.79 (1H, dd, J = 10.3, 4.5 Hz), 1.88 (1H, m), 1.51 (3H, d, J = 6.6 Hz), 1.45 (1H, m), 1.26 (1H, m), 0.89 (1H, m)
Example321	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, d, J = 2.2 Hz), 7.59 (1H, dd, J = 8.0, 1.9 Hz), 7.29-7.24 (2H, m), 6.95 (1H, t, J = 7.3 Hz), 6.87-6.82 (3H, m), 5.80 (1H, brd, J = 8.1 Hz), 5.11 (1H, m), 4.75 (2H, q, J = 8.8 Hz), 4.05 (1H, dd, J = 10.2, 5.9 Hz), 3.81 (1H, dd, J = 10.2, 7.4 Hz), 1.84 (1H, m), 1.51 (3H, d, J = 6.6 Hz), 1.45 (1H, m), 1.30 (1H, m), 0.93 (1H, m)
Example322	^{1}H-NMR (300 MHz, $CDDCl_3$) δ 8.99 (1H, brs), 8.32 (1H, s), 8.14 (1H, s), 7.53 (1H, d, J = 8.1 Hz), 7.24 (1H, m), 7.04 (1H, t, J = 7.3 Hz), 6.85 (1H, d, J = 7.3 Hz), 6.58 (1H, t, J = 2.2 Hz), 6.51 (1H, brd, J = 7.4 Hz), 5.29 (1H, m), 4.84-4.70 (2H, m), 2.55 (1H, m), 1.71-1.61 (2H, m), 1.52 (3H, d, J = 6.6 Hz), 1.44 (1H, m)
Example323	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.71 (1H, brs), 8.31 (1H, s), 8.11 (1H, s), 7.54 (1H, d, J = 7.3 Hz), 7.06 (1H, t, J = 10.3 Hz), 6.83 (1H, d, J = 7.3 Hz), 6.64-6.55 (3H, m), 5.28 (1H, m), 4.77 (2H, q, J = 8.1 Hz), 2.73 (1H, m), 1.75 (1H, m), 1.58 (1H, m), 1.52 (3H, d, J = 6.6 Hz), 1.37 (1H, m)
Example324	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, s), 8.00 (1H, d, J = 8.0 Hz), 7.92 (1H, d, J = 8.8 Hz), 7.75 (1H, d, J = 8.1 Hz), 7.66 (1H, t, J = 7.3 Hz), 7.45 (1H, t, J = 7.3 Hz), 7.33 (1H, d, J = 8.0 Hz), 7.22 (2H, d, J = 1.4 Hz), 6.96 (1H, brd, J = 7.3 Hz), 5.18 (1H, m), 4.36 (2H, q, J = 8.0 Hz), 2.73 (1H, m), 2.33 (1H, m), 1.70 (2H, t, J = 7.3 Hz), 1.48 (3H, d, J = 6.5 Hz)
Example325	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, t, J = 2.2 Hz), 8.04 (1H, d, J = 8.0 Hz), 7.93 (1H, d, J = 8.8 Hz), 7.77 (1H, d, J = 8.1 Hz), 7.66 (1H, m), 7.39 (1H, d, J = 8.1 Hz), 7.30-7.22 (2H, m), 6.99 (1H, brd, J = 7.3 Hz), 5.18 (1H, m), 4.40 (2H, q, J = 8.0 Hz), 2.78 (1H, m), 2.36 (1H, m), 1.65 (2H, t, J = 7.3 Hz), 1.45 (3H, d, 6.6 Hz)
Example328	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (1H, s), 7.19-7.11 (3H, m), 6.99-6.85 (4H, m), 5.12 (1H, m), 3.82 (2H, d, J = 7.3 Hz), 2.43 (1H, m), 2.30 (3H, s), 1.65 (1H, m), 1.49 (1H, m), 1.45 (3H, d, J = 6.6 Hz), 1.40-1.20 (2H, m), 0.66 (2H, m), 0.35 (2H, m)
Example327	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.26-7.21 (2H, m), 7.03-76.92 (2H, m), 6.85 (1H, m), 6.66 (1H, m), 6.17(1H, m), 4.40 (2H, q, J = 8.1 Hz), 2.64 (1H, m), 1.75 (1H, m), 1.60 (1H, m), 1.47 (3H, d, J = 6.6 Hz), 1.22 (1H, m)
Example328	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, s), 7.26-7.21 (2H, m), 6.99-6.89 (2H, m), 6.82 (1H, m), 6.64 (1H, m), 5.17 (1H, m), 4.39 (2H, q, J = 8.0 Hz), 2.58 (1H, m), 1.75 (1H, m), 1.65 (1H, m), 1.47 (3H, 6.6 Hz), 1.26 (1H, m)
Example345	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, m), 7.48-7.17 (7H, m), 6.90 (1H, d, J = 7.3 Hz), 6.82 (1H, m), 6.74 (1H, s), 6.73 (1H, d, J = 7.3 Hz), 5.17 (1H, m), 5.07 (2H, s), 4.41 (2H, q, J = 8.0 Hz), 2.50 (1H, m), 1.70 (1H, m), 1.60 (1H, m), 1.46 (3H, d, J = 6.6 Hz), 1.21 (1H, m)
Example346	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, d, J = 1.5 Hz), 7.45-7.15 (7H, m), 6.90 (1H, d, J = 7.3 Hz), 6.80 (1H, m), 6.71 (1H, s), 6.69 (1H, d, J = 7.3 Hz), 5.17 (1H, m), 5.04 (2H, s), 4.40 (2H, q, J = 8.1 Hz), 2.44 (1H, m), 1.72-1.60 (2H, m), 1.47 (3H, d, J = 6.6 Hz), 1.26 (1H, m)
Example347	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.45-7.22 (6H, m), 7.04 (2H, d, J = 8.8 Hz), 6.91 (2H, d, J = 8.8 Hz), 6.87 (1H, m), 5.17 (1H, m), 5.07 (2H, s), 4.40 (2H, q, J = 8.1 Hz), 2.48 (1H, m), 1.66-1.52 (2H, m), 1.46 (3H, d, J = 6.6 Hz), 1.17 (1H, m)
Example348	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, m), 7.47-7.21 (6H, m), 7.01 (2H, d, J = 8.0 Hz), 6.89 (1H, m), 6.88 (2H, d, J = 8.0 Hz), 5.17 (1H, m), 5.05 (2H, s), 4.40 (2H, q, J = 8.1 Hz), 2.44 (1H, m), 1.69-1.60 (2H, m), 1.47 (3H, d, J = 6.6 Hz), 1.22 (1H, m)
Example349	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, s), 7.28-7.25 (2H, m), 6.95-6.87 (2H, m), 6.65-6.58 (2H, m), 5.18 (1H, m),4.41 (2H, q, J = 8.1 Hz), 3.80 (3H, s), 2.56 (1H, m), 1.69 (1H, m), 1.54 (1H, m), 1.48 (3H, d, J = 6.6 Hz), 1.20 (1H, m)
Example350	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, m), 7.31-7.25 (2H, m), 6.93-6.86 (2H, m), 6.63-6.54 (2H, m), 5.19 (1H, m),4.41 (2H, q, J = 8.0 Hz), 3.77 (3H, s), 2.51 (1H, m), 1.69 (1H, m), 1.59 (1H, m), 1.48 (3H, d, J = 6.6 Hz), 1.24 (1H, m)
Example351	^{1}H-NMR(300 MHz, $CDCl_3$) δ 8.30 (1H, m), 7.29-7.25 (2H, m), 7.15 (1H, m), 7.03 (1H, m), 7.00-6.88 (2H, m), 5.21 (1H, m), 4.41 (2H, q, J = 8.1 Hz), 2.66 (1H, m), 1.65-1.53 (2H, m), 1.49 (3H, d, J = 6.6 Hz), 1.20 (1H, m)
Example352	^{1}H-NMR(300 MHz, $CDCl_3$) δ 8.30 (1H, m), 7.36-6.87 (6H, m), 5.20 (1H, m), 4.41 (2H, q, J = 8.1 Hz), 2.59 (1H, m), 1.73-1.47 (2H, m), 1.46 (3H, d, J = 6.6 Hz), 1.26 (1H, m)
Example353	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, m), 7.33-7.11 (7H, m), 6.90 (1H, d, J = 7.3 Hz), 5.18 (1H, m), 4.41 (2H, q, J = 8.0 Hz), 2.53 (1H, m), 1.72 (1H, m), 1.60 (1H, m), 1.46 (3H, d, J = 6.6 Hz), 1.22 (1H, m)
Example354	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (1H, m), 7.29-7.06 (7H, m), 6.90 (1H, d, J = 7.3 Hz), 5.18 (1H, m), 4.39 (2H, q, J = 8.0 Hz), 2.47 (1H, m), 1.73-1.61 (2H, m), 1.47 (3H, d, J = 6.6 Hz), 1.27 (1H, m)
Example357	^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (1H, d, J = 2.2 Hz), 7.27-7.14 (3H, m), 6.89 (1H, brd, J = 7.3 Hz), 6.74-6.62 (3H, m), 5.16 (1H, m), 4.39 (2H, q, J = 8.1 Hz), 3.78 (3H, s), 2.44 (1H, m), 1.72-1.59 (2H, m), 1.46 (3H, d, J = 7.3 Hz), 1.26 (1H, m)

Pharmacological Assays

In Vitro Human T-Type Ca^{2+} Channel Activity

T-type calcium channel activity of compounds was determined by methodology well known in the art, including the "Ca^{2+} influx Assay" and the "T-type Ca^{2+} Blocker Voltage-Clamp Assay".

Ca^{2+} Influx Assay

Inhibition of T-type calcium channel activity was determined by cell-based flu-orescent Ca^{2+} influx assay, in which potassium ionophore was added to decrease resting membrane potential and extra-cellular high-K^+ stimulation was used to modulate the membrane potential of the cell. The changes in fluorescent signal were monitored by the cell imaging technology by Hamamatsu Photonics's Functional Drug Screening System (FDSS).

Cell Maintenance:

HEK 293 cells expressing the human T-type channel alpha-1H (CaV 3.2) were maintained in DMEM supplemented with 10% heat-inactivated FBS, 100 units/ml Penicillin, 100 microg/ml Streptomycin, 150 microg/ml Zeocin, 300 microg/ml Geneticin. The cells were grown in a 5% CO_2 humidified incubator at 37° C.

Assay Protocol:

Day One:

1. Cells were harvested and seeded in a poly-D-lysine coated black-sided clear bottom 384-well plate at density of 10,000 cells/well at 24 hours prior to assay.

2. Incubate at 37° C. in 5% CO_2.

Day Two:

1. Wash each well with assay buffer (see below) and leave 20 $_R$I using plate washer, ELx-405 Select CW (BIO-TEK).
2. Add 20 μL of assay buffer containing 6 μM Fluo-4-AM (Molecular Probes) and 0.005% Pluronic F-127 to each well.
3. Incubate the plate at 37° C. for 1 hour.
4. Wash each well assay buffer (see below) and leave 20 μl using plate washer, ELx-405 Select CW (BIO-TEK).
5. Add 10 μl of compound solution into each well by FDSS6000 and leave the plate for 4.5 min, and then add 10 μl of potassium ionophore solution.
6. Add 20 μl of high-K^+ depolarizing solution (see below) and monitor the change of fluorescent signal.

The IC_{50} values for compounds of the present invention were determined from 7-point dose-response studies. Curves were generated using the average of duplicate wells for each data point. Finally, the IC_{50} values are calculated with the best-fit dose curve determined by XLfit.

TABLE 5

Assay buffer (pH 7.4, Adjusted by HCl)

Reagent	Final conc. (mM)	Volume (mL)
NMDG (1.4M)	140	100
KCl (1.17M)	5	4.25
$MgCl_2$ (80 mM)	1	12.5
Glucose (0.5M)	5	10
$CaCl_2$ (1M)	1	1
HEPES buffer (1M)	16	16
MQ water	—	856.25

TABLE 6

High-K^+ depolarizing solution

Reagent	Final conc. (mM)	Volume (mL)
KCl (1.17M)	90	83.3
$MgSO_4$ (1M)	0.5	0.5
KH_2PO_4 (1M)	1.2	1.2
Glucose (0.5M)	11.7	23.4
$CaCl_2$ (1M)	2	2
HEPES buffer (1M)	18.4	18.4
MQ water	—	871.2

Electrophysiology Assay for T-type Ca^{2+}

In a typical experiment ion channel function from HEK 293 cells expressing the human T-type channel alpha-1H (CaV 3.2) is recorded to determine the activity of compounds in blocking the calcium current mediated by the T-type channel. Cells expressing the T-type channels were grown in growth media which comprised: DMEM, 10% heat-inactivated FBS, 100 units/ml Penicillin, 100 mg/ml Streptomycin, 150 mg/ml Zeocin, 300 mg/ml Geneticin. T-type Ca channel expressing HEK293 cells were dissociated by 0.05% Trypsine-EDTA, and then seeded on cover glass for 24 hr.

Glass pipettes are pulled to a tip diameter of 1-2 micrometer on a pipette puller. The pipettes are filled with the intracellular solution and a chloridized silver wire is inserted along its length, which is then connected to the headstage of the voltage-clamp amplifier. The extracellular recording solution consists of (mM): 150 mM NMDG, 2 mM $CaCl_2$, 10 mM HEPES, 10 mM Glucose, pH 7.4. The internal solution consists of (mM): 110 CsF, 10 EGTA, 10 HEPES, 3 ATP-Mg, 0.6 GTP pH 7.2; Upon insertion of the pipette tip into the bath, the series resistance is noted (acceptable range is between 1-4 megaohm). The junction potential between the pipette and bath solutions is zeroed on the amplifier. The cell is then patched, the patch broken, and, after compensation for series resistance (>=80%), the voltage protocol is applied while recording the whole cell Ca^{2+} current response. Voltage protocols: (1) −80 mV holding potential every 30 seconds pulse to −20 mV for 100 msec duration; the effectiveness of the drug in inhibiting the current mediated by the channel is measured directly from measuring the reduction in peak current amplitude initiated by the voltage shift from −80 mV to −20 mV; (2). −140 mV holding potential every 30 seconds pulse to −20 mV for 100 msec duration; the effectiveness of the drug in inhibiting the current mediated by the channel is measured directly from measuring the reduction in peak current amplitude initiated by the shift in potential from −140 mV to −20 mV. The difference in block at the two holding potentials was used to determine the effect of drug at differing levels of inactivation induced by the level of resting state potential of the cells. After obtaining control baseline calcium currents, extracellular solutions containing increasing concentrations of a test compound are washed on. Once steady state inhibition at a given compound concentration is reached, a higher concentration of compound is applied. % inhibition of the peak inward control Ca^{2+} current during the depolarizing step to −20 mV is plotted as a function of compound concentration.

(3) The normalized steady-steady inactivation curve is constructed using 5 sec (for vehicle) or 60 sec (for drugs) conditioning pulse to different potentials followed immediately by the test pulse to −20 mV. Peak currents are plotted as fraction of the maximum current at the conditioning potentials ranging from −140 mV to −20 mV. V1/2 or k values are estimated from Boltzmann fits. The affinity of drugs to resting state of T-type Ca channels ($K_{resting}$ or Kr) is assessed by 30 msec test pulse from a negative holding potential of −140 mV, where virtually all channels are in the resting state. K_r value is calculated by a conventional 1:1 binding model:

$$K_{resting}(Kr)=\{[\text{drug}]I\text{max,drug}/(I\text{max, control-}I\text{max, drug})\}$$

where $K_{resting}$ (=K_r) is a dissociation constant for the resting state and [drug] is compound concentration. I_{max}, control and I_{max}, drug are peak currents in the absence and presence of compound, respectively.

The affinity of drug to inactivated state of T-type Ca channels (K_{inact} or Ki) is estimated from the shift of the availability curve by compound. Interaction of the compound with the inactivated state channel is evaluated as suggested by Bean et al (1983 Journal of general pharmacology 81, 613-) by fitting experimental points of the compound-induced steady-state inactivation mid-point potential shifts to the equation:

$$K_{inact}(Ki)=\{[\text{drug}]/((1+[\text{drug}]/Kr)*\exp(-\Delta V/k)-1)\} \quad \text{[Math.1]}$$

where K_{inact} (=K_i) is a dissociation constant for the inactivated state. AV is the compound-induced voltage shift of half maximal voltage of Boltzmann curve and k is the slope factor of compound.

All examples of the invention have an IC_{50}=<1 microM in the Ca^{2+} Influx Assay or IC_{50}=<3 microM in $Na_{V1.3}$ FRET Assays or $Na_{V1.7}$ FRET Assays.

Especially, Example 3, Example 33, Example 57, Example 104, Example 106, Example 108, Example 110, Example 111, Example 124, Example 125, Example 133, Example 134, Example 147, Example 167, Example 168, Example 169, Example 171, Example 172, Example 181, Example 182, Example 190, Example 193, Example 194, Example 202, Example 203, Example 204, Example 205, Example

206, Example 207, Example 208, Example 210, Example 211, Example 212, Example 213, Example 222, Example 223, Example 224, Example 225, Example 226, Example 227, Example 228, Example 229, Example 237, Example 240, Example 243, Example 244, Example 245, Example 246, Example 248, Example 250, Example 251, Example 253, Example 258, Example 259, Example 260, Example 261, Example 263, Example 266, Example 267, Example 268, Example 270, Example 271, Example 273, Example 275, Example 276, Example 277, Example 279, Example 280, Example 282, Example 284, Example 286, Example 287, Example 289, Example 294, Example 296, Example 305, Example 306, Example 307, Example 309, Example 310, Example 316, Example 317, Example 318, Example 320, Example 322, Example 323, Example 325, Example 327, and Example 346 of the invention have an IC_{50}=<0.3 microM in the Ca^{2+} Influx assay.

In Vitro Human Voltage Gated Sodium Channels Activity

Voltage gated sodium channels activity of compounds was determined by methodology well known in the art.

The ability of the aryl substituted carboxamid derivatives of the formula (I) to inhibit the $Na_{V1.3}$,$Na_{V1.7}$ and $Na_{V1.5}$ channels was measured by FRET assay and electrophysiology assay described below.

FRET Assay for Navs

This screen is used to determine the effects of compounds on human $Na_{V1.3}$, human $Na_{V1.7}$, and human $Na_{V1.5}$ channels, utilising the cell imaging technology by Hamamatsu Photonics's Functional Drug Screening System (FDSS). This experiment is based on FRET (Fluorescence Resonance Energy Transfer) and uses two fluorescent molecules. The first molecule, Oxonol (DiSBAC2(3)), is a highly fluorescent, negatively charged, and hydrophobic ion that "senses" the trans-membrane electrical potential. In response to changes in membrane potential, it can rapidly redistribute between two binding sites on opposite sides of the plasma membrane. The voltage dependent redistribution is transduced into a ratiometric fluorescent readout via a second fluorescent molecule (Coumarin (CC2-DMPE)) that binds specifically to one face of the plasma membrane and functions as a FRET partner to the mobile voltage-sensing ion. To enable the assay to work, the channels have to be pharmacologically held in the open state. This is achieved by treating the cells with veratridine.

Cell Maintenance:

Each HEK293 cells expressing human $Na_{V1.3}$ channels and HEK293 cells expressing human $Na_{V1.5}$ channels were grown in T225 flasks, in a 5% CO_2 humidified incubator to about 80% confluence. Media composition consisted of Dulbecco's Modified Eagle Medium (high glucose), 10% fetal calf serum (FCS), 100 units/ml Penicillin, 100 microg/ml Streptomycin and 500 microg/ml Geneticine.

CHO cells expressing human $Na_{V1.7}$ channels were grown in T225 flasks, in a 5% CO_2 humidified incubator to about 80% confluence. Media composition consisted of HAM/F12 with Glutamax I, 10% fetal calf serum (FCS), 100 units/ml Penicillin and 100 microg/ml Hygromycin.

Protocol:

Seed each cell lines (1.5×10^4 cells/well) into poly-D-lysine coated 384-well plates prior to experimentation.

Incubate at 37° C. in 5% CO_2 for 24 hours.

Wash each well with buffer #1 (140 mM NaCl, 4.5 mM KCl, 10 mM D-Glucose, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, pH 7.4 adjusted with NaOH) twice using plate washer.

Add 1st loading solution containing 5 μM CC2-DMPE and 0.02% Pluronic F-127 in buffer #1.

Incubate the plate at room temperature in dark for 0.5 hours.

Wash each well with buffer #2 (160 mM Choline, 10 mM D-Glucose, 0.1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, pH 7.4 adjusted with KOH) twice using plate washer.

Add 2nd loading solution containing 15 μM DiSBAC2(3), 0.5 mM VABSC-1, 10 μM veratridine and 0.004% Pluronic F-127 in buffer #2.

Add compound solutions into the assay plate and leave the plate for 30 minutes under the dark at room temperature.

Measure by FDSS.

The data was analyzed and reported as normalized ratios of intensities measured in the 465 nm and 575 nm channels. The process of calculating these ratios was performed as follows:

"FI465B"=the mean of fluorescence intensity as baseline (before Na+ligand addition) at 465nm

"FI575B"=the mean of fluorescence intensity as baseline (before Na+ligand addition) at 575nm

"FI465Max"=maximum fluorescence intensity at 465nm after Na+stimulation

"FI575Min"=minimum fluorescence intensity at 575nm after Na+stimulation

"FR"=fluorescence ratio=(FI465Max/FI575Min)−(FI465B/FI575B)

[Math. 2]

$$\text{Inhibition}(\%) = 100 - \frac{(FR \text{ of each well}) - (\text{median } FR \text{ in positive controls})}{(\text{median } FR \text{ in negative controls}) - (\text{median } FR \text{ in positive controls})} \times 100$$

This analysis is performed using a computerized specific program designed for FDSS generated data. Fluorescence ratio values are plotted using XLfit to determine an IC_{50} value for each compound.

Electrophysiology Assay for Navs

Whole cell patch clamp recording was used to assess the efficacy or selectivity of Na channel blocker on human $NO_{V1.3}$ (hSCN3A) expressing HEK293 cells or human $NO_{V1.7}$ (hSCN9A) expressing CHO cells. Human $NO_{V1.3}$ expressing HEK293 cells were grown in growth media which comprised: DMEM, 10% heat-inactivated FBS (Hyclone Laboratories Inc), 100 microgram/ml Penicillin/100 U/ml Streptomycin, 150 microgram/ml Zeocin, 3 microgram/ml Geneticin. Human NO_{V7}, expressing CHO cells were grown in growth media which comprised: HAM/F-12, 9% heat-inactivated FBS (Hyclone Laboratories Inc), 100 microgram/ml Penicillin/100 U/ml Streptomycin, 100 microgram/ml Hygromycin.

Na channel expressing cells were dissociated by 0.05% Trypsine-EDTA, and then seeded on cover glass for 24-48 hr.

Glass pipettes were pulled to a tip diameter of 1-2 micrometer on a pipette puller. The pipettes were filled with the intracellular solution and a chloridized silver wire was inserted along its length, which was then connected to the headstage of the voltage-clamp amplifier (Axon Instruments or HEKA electronik). The extracellular recording solution consists of (mM): 140 NaCl, 5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES, 10 Glucose, pH 7.4 adjusted with NaOH. The internal solution consists of (mM): 120 CsF, 15 NaCl, 10 EGTA,

10 HEPES, pH 7.2 adjusted with CsOH; Upon insertion of the pipette tip into the bath, the pipette resistance was noted (acceptable range is between 1-3 megaohm). The junction potential between the pipette and bath solutions was zeroed on the amplifier. After establishing the whole-cell configuration, approximately 10 minutes were allowed for the pipette solution to equilibrate within the cell before beginning recording. Currents were lowpass filtered between 2-5 kHz and digitally sampled at 10 kHz. Series resistance was compensated (>80%) and was monitored continuously.

The normalized steady-steady inactivation curve was constructed using 5 sec (for vehicle) or 60 sec (for drugs) conditioning pulse to different potentials followed immediately by the test pulse to 0mV. Peak currents were plotted as fraction of the maximum current at the conditioning potentials ranging from −120 mV to −40 mV. V1/2 or k values were estimated from Boltzmann fits. The affinity of drugs to resting state of Na channels ($K_{resting}$ or Kr) was assessed by 30 msec test pulse from a negative holding potential of −120 mV, where virtually all channels are in the resting state. K_r value was calculated by a conventional 1:1 binding model:

$$K_{resting}(Kr)=\{[\text{drug}]I\text{max,drug}/(I\text{max,control}-I\text{max,drug})\}$$

where $K_{resting}$ (=K_r) is a dissociation constant for the resting state and [drug] is compound concentration. I_{max}, control and I_{max}, drug are peak currents in the absence and presence of compound, respectively.

The affinity of drug to inactivated state of Na channels (K_{inact} or Ki) was estimated from the shift of the availability curve by compound. Interaction of the compound with the channel on inactivated state was evaluated by the following equation:

$$K_{inact}(Ki)=\{[\text{drug}]/((1+[\text{drug}]/Kr)*\exp(-\Delta V/k)-1)\} \quad \text{[Math.3]}$$

where K_{inact} (=K_1) is a dissociation constant for the inactivated state. ΔV is the compound-induced voltage shift of half maximal voltage of Boltzmann curve and k is the slope factor on presence of compound.

The compounds of the examples were tested in the above-described assay. The results are as follows:

All examples of the invention have an IC_{50}=<1 microM in the Ca^{2+} Influx Assay or IC_{50}=<3 microM in $Na_{V1.3}$ FRET or $Na_{V1.7}$ FRET Assays.

Especially, Example 1, Example 4, Example 5, Example 6, Example 9, Example 10, Example 11, Example 12, Example 13, Example 14, Example 15, Example 16, Example 18, Example 20, Example 21, Example 22, Example 23, Example 28, Example 29, Example 32, Example 36, Example 37, Example 41, Example 42, Example 44, Example 45, Example 48, Example 51, Example 52, Example 53, Example 54, Example 56, Example 59, Example 62, Example 63, Example 64, Example 65, Example 66, Example 67, Example 68, Example 69, Example 70, Example 74, Example 75, Example 76, Example 77, Example 78, Example 80, Example 82, Example 85, Example 86, Example 87, Example 88, Example 89, Example 90, Example 91, Example 92, Example 93, Example 94, Example 95, Example 99, Example 102, Example 103, Example 113, Example 130, Example 131, Example 138, Example 143, Example 146, Example 150, Example 151, Example 152, Example 154, Example 156, Example 157, Example 158, Example 161, Example 162, Example 175, Example 184, Example 192, Example 195, Example 196, Example 197, Example 201, Example 209, Example 214, Example 220, Example 238, Example 241, Example 269, Example 274, Example 285, Example 308, Example 313, Example 314, Example 315, Example 321, Example 324, Example 326, Example 328, Example 332, Example 333, Example 337, Example 338, Example 339, Example 341, Example 345, Example 359, Example 377, Example 424, Example 3, Example 57, Example 104, Example 124, Example 125, Example 147, Example 169, Example 182, Example 194, Example 202, Example 204, Example 205, Example 206, Example 208, Example 210, Example 211, Example 212, Example 213, Example 226, Example 240, Example 246, Example 248, Example 251, Example 253, Example 261, Example 267, Example 268, Example 273, Example 279, Example 294, Example 306, Example 307, Example 310, Example 316, Example 317, Example 318, Example 320, Example 322, Example 323, Example 325, Example 327, Example 346, Example 329, Example 347, Example 355, Example 386, Example 396, Example 397, Example 399, Example 400, Example 413, Example 415, Example 417, Example 419, Example 420, Example 427, Example 431, Example 432, Example 434, Example 439, Example 440, Example 441, Example 442, Example 443, Example 444, Example 447, Example 448, Example 449, Example 454, Example 455, Example 456, and Example 458 of the invention have an IC_{50}=<1.0 microM in $Na_{V1.3}$ FRET or $Na_{V1.7}$ FRET Assays.

In Vivo Assay

Chronic constriction injury (CCI)-induced static allodynia

Male Sprague-Dawley rats weighing 210-240 g were purchased from Charles River Japan (Kanagawa, Japan). Animals were housed in groups of two under a 12-h light/dark cycle (lights on at 07:00) with access to food and water ad libitum. The CCI was made according to the method of Bennett GJ and Xie YK (Pain 1988, 33: 87-107). Animals were anesthetized with intraperitoneal injection of sodium pentobarbital. The left common sciatic nerve was exposed at the level of the middle of the thigh and four ligatures were loosely tided around it by using 4-0 silk thread (Ethicon Inc, Brussels, Belgium) with approximately 1 mm apart. The incision was sutured, and the rats were allowed to recover. Sham operation was performed in the same manner except of sciatic nerve ligation. After 2 to 3 weeks, static allodynia was assessed using von Frey hairs (VFHs; North Coast Medical Inc., San Jose, Calif.) as described by Field M J et al. (Pain 1999, 83: 303-311). The animals were placed in grid bottom cages and allowed to acclimate for at least 30 min prior to the start of experiment. VFHs in ascending order of force (0.16, 0.4, 0.6, 1, 1.4, 2, 4, 6, 8, 10, 15 and 26 g) were applied to the plantar surface of the hind paw. Each VFH was applied to the ipsilateral paw for 6 seconds or until a withdrawal response occurred. Once a withdrawal response was happened, the paw was re-tested, starting with the next descending VFH until no response was occurred. The lowest amount of force required to elicit a response was defined as paw withdrawal threshold (PWT) in g. Animals with <2 g of PWTs were selected for evaluation and randomized to be nearly equal across all groups. The compounds of the invention or their vehicles were administered systemically. All tested compounds of the invention showed potent activities in this model.

Complete Freund's Adjuvant (CFA)-induced thermal hyperalgesia

Male Sprague-Dawley rats weighing 200-250 g were purchased from Charles River Japan (Kanagawa, Japan). Animals were housed under a 12-h light/dark cycle (lights on at 07:00) with access to food and water ad libitum. CFA-induced thermal hyperalgesia was assessed using the plantar test apparatus (Ugo Basile, Verse, Italy) as describe by Hargreaves K et al. (Pain 1988, 32: 77-88). Animals were placed in an apparatus consisting of individual testing box on an elevated glass table and allowed to acclimate for at least 10

min. Following habituation, a mobile radiant heat source was located under the table and heat stimulation was applied to the plantar surface of the right hind paw. The latency to remove its hind paw was defined as paw withdrawal latency (PWL) in sec. CFA was prepared at a concentration of 200 microg/100 microl of *Mycobacterium tuberculosis* H37 RA (Difco Laboratories Inc.) in liquid paraffin and injected into the plantar surface of the right hind paw. PWL was measured before and 2 days after CFA injection. Animals showing decrease of the PWL on day 2 were selected for evaluation and randomized to be nearly equal across all groups. The compounds of the invention or their vehicles were administered systemically. PWLs were measured at the appropriated time after compound administration.

Metabolic Stability Assay:

Half-life in human liver microsomes (HLM)

Test compounds (1 microM) were incubated with 3.3 mM $MgCl_2$ and 0.78 mg/mL HLM (HL101) in 100 mM potassium phosphate buffer (pH 7.4) at 37° C. on the 96-deep well plate. The reaction mixture was split into two groups, a non-P450 and a P450 group. NADPH was only added to the reaction mixture of the P450 group. (NADPH generation system was also used instead of NADPH.) An aliquot of samples of P450 group was collected at 0, 10, 30, and 60 min time point, where 0 min time point indicated the time when NADPH was added into the reaction mixture of P450 group. An aliquot of samples of non-P450 group was collected at −10 and 65 min time point. Collected aliquots were extracted with acetonitrile solution containing an internal standard. The precipitated protein was spun down in centrifuge (2000 rpm, 15 min). The compound concentration in supernatant was measured by LC/MS/MS system.

The half-life value was obtained by plotting the natural logarithm of the peak area ratio of compounds/internal standard versus time. The slope of the line of best fit through the points yields the rate of metabolism (k). This was converted to a half-life value using following equations: Half-life=1n 2/k

Drug-drug Interaction Assay

This method essentially involves determining the percent inhibition of metabolites formation from probes (Tacrine (Sigma A3773-1G) 2 microM, Dextromethorphan (Sigma D-9684) 5 microM, Diclofenac (Sigma D-6899-10G) 5 microM, and Midazolam(ULTRAFINE UC-429) 2 microM) at 3 microM of the each compound.

More specifically, the assay is carried out as follows. The compounds (60 microM, 10 microL) were pre-incubated in 170 microL of mixture including human liver microsomes, 100 mM potassium phosphate buffer and probes as substrate for 5 min. Reaction was started by adding a NADPH (10 mM, 20 microL) (NADPH generating system, which consist of 0.5 mM NADP, 10 mM $MgCl_2$, 6.2 mM DL-lsocitric acid and 0.5 U/ml Isocitric Dehydrogenase, was also used). The assay plate was incubated at 37° C. Acetonitril was added to the incubate solution at appropriate time (e.g. 8 min).

The metabolites' concentration in the supernatant was measured by LC/MS/MS system.

The degree of drug interaction was interpreted based on generation % of metabolites in the presence or absence of test compound.

Human Dofetilide Binding Assay

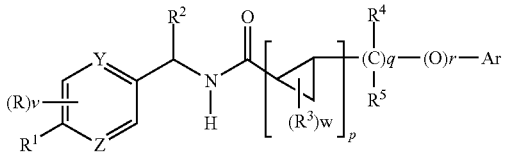
Human HERG transfected HEK293S cells were prepared and grown in-house. The collected cells were suspended in 50 mM Tris-HCl, 10 mM KCl, 1 mM $MgCl_2$, Complete (Roche) (pH 7.4 at 4° C.) and homogenized using a hand held Polytron PT 1300 D disruptor set at 15,000 rpm for 20 sec on ice. The homogenates were centrifuged at 48,000×g at 4° C. for 20 min. The pellets were then resuspended, homogenized, and centrifuged once more in the same manner. The final pellets were re-suspended in an appropriate volume of 50 mM Tris-HCl, 10 mM KCl, 1 mM $MgCl_2$, Complete (pH 7.4 at 4° C.), homogenized, aliquoted and stored at −80° C. until use. An aliquot of membrane fractions was used for protein concentration determination using BCA protein assay kit (PIERCE) and ARVOsx plate reader (Wallac). Binding assays were conducted in a total volume of 30 microL in 384-well plates. The activity was measured by PHERAstar (BMG LABTECH) using fluorescence polarization technology. Ten microL of test compounds were incubated with 10 microL of fluorescence ligand (6 nM Cy3B tagged dofetilide derivative) and 10 microL of membrane homogenate (6 microg protein) for 120 minutes at room temperature. Nonspecific binding was determined by 10 microM E4031 at the final concentration. The IC_{50} values were calculated using Dose Response One Site Models, 4 Parameter Logistic Model (XLfit).

All publications, including but not limited to, issued patents, patent applications, and journal articles, cited in this application are each herein incorporated by reference in their entirety. Although the invention has been described above with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

The invention claimed is:

1. A compound of the formula (II)

(II)



wherein

R is halogen, or C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl;

v is 0, 1, 2, or 3; when v is two or more than two, R may be same or different;

R^1 is —OCH_2CF_3 or —OCH_3;

R^2 is C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl;

R^3 is independently selected from the group consisting of: (1) halogen, (2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^6, (3) C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^6, (4) —O—C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^6, (5) —O—C_{3-6} cycloalkyl, which is unsubstituted or substituted with one or more substituents independently selected from R^6, and (6) —NR^7R^8;

w is 0, 1, 2, 3 or 4; when w is two or more than two, R^3 may be same or different;

R^4 and R^5 are independently hydrogen, halogen, or C_{1-6} alkyl which is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl;

R^6 is independently selected from the group consisting of: (1) hydrogen, (2) hydroxyl, (3) halogen, (4) —O_1R^7, (5) —CN, (6) —(C═O)—NR^7R^8, (7) —NR^7R^8, (8) —$S(O)_2$—NR^7R^8, (9) —$S(O)_t$—R^7, where t is 0, 1 or 2, (10) —CN, and (11) —NO_2;

wherein 1 is 0 or 1; when 1 is 0, a chemical bond is present in the place of O_1;

R^7 and R^8 are independently hydrogen, C_{1-6} alkyl, or C_{3-8} cycloalkyl, which are unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, and —O—C_{1-6} alkyl; or R^7 form a 4 to 7 membered ring with R^8 which may contain nitrogen atom, or oxygen atom, wherein the 4 to 7 membered ring is optionally substituted with 1 to 6 substituents independently selected from the group consisting of: (1) hydrogen, (2) hydroxyl, (3) halogen, (4) C_{1-6} alkyl, and (5) —O—C_{1-6} alkyl;

p is 1; q, and r are independently 0 or 1;

Y and Z are independently selected from nitrogen atom and carbon atom; Y and Z are not carbon atom at the same time;

wherein n is 0 or 1, when n is 0, a chemical bond is present in the place of O_n;

Ar is aryl which is optionally substituted with 1 to 5 substituents independently selected from the group consisting of:

(1) halogen, (2) hydroxyl, (3) —O_n-heterocyclic group, where the heterocyclic group is unsubstituted or substituted with one or more substituents independently selected from R^6, (4) —O_n—C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from R^6, (5) —O_n—C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from R^6, (6) —NR^7R^8, (7) —$S(O)_2$—N R^7R^8, (8) —$S(O)_t$—R^7, where t is 0, 1 or 2, (9) —NR^7SO_2 R^8, (10) —(C═O)—NR^7R^8 , (11) —NR^7(C═O)R^8, (12) —CN, and (13) —NO_2;

wherein n is 0 or 1; when n is 0, a chemical bond is present in the place of O_n;

or a pharmaceutically acceptable salt thereof.

2. The compound as claimed in claim **1**, wherein R^3 is independently selected from the group consisting of:

(1) halogen, and (2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more substituents independently selected from halogen;

R^4 and R^5 are independently hydrogen, halogen, or C_{1-6} alkyl which is unsubstituted or substituted with one or more substituents independently selected from halogen;

wherein n is 0 or 1; when n is 0, a chemical bond is present in the place of O_n;

Ar is aryl which is optionally substituted with 1 to 5 substituents independently selected from the group consisting of:

(1) halogen, (2) hydroxyl, (3) —$O_{n—C\ 1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, (4) —O_n—C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, and (5) —CN;

wherein n is 0 or 1; when n is 0, a chemical bond is present in the place of O_n;

or a pharmaceutically acceptable salt thereof.

3. The compound selected from:

(1R,2R)-2-methyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxamide;

(R)-N-(1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-3-(6-fluoro-1H-indol-1-yl)propanamide;

(1R,2R)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxamide;

trans-2-(7-fluoro-1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(1H-indol-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(1H-indol-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-7-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(isoquinolin-3-yl)-N-((R)-1-(5(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-3-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2((4-chlorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(2-fluoro-5-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2((1H-indol-1-yl)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(2,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(2,5-difluorophenyl)cyclopropanecarboxamide;

trans-2-(2,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(1H-indol-4-yl)cyclopropanecarboxamide;

trans-2(4-methoxy-3-methylphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(1H-indol-6-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

trans-2-(5-fluoro-1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

trans-2-(quinolin-3-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

trans-2(1H-indol-4-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(8chloroquinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2(1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(1H-indol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(1H-indol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

trans-2-(1-methyl-1H-indazol-6-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(4-(benzyloxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(R,E)-3-(quinolin-2-yl)-N-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)acrylamide;

(1S*,2S*)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(3,5-difluorophenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(3-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(4-methoxyphenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(2-chloro-4-fluorophenyl)-N-((R)-1-(5-cyclopropylmethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2(2-fluoro-4-methoxyphenyl)cyclopropanecarboxamide;

(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl)cyclopropanecarboxamide;

(1S*,2S*)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-2-(2,4,6-trifluorophenyl)cyclopropanecarboxamide;

(1R*,2R*)-N-((R)-1-5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)-2(2,4,6-trifluorophenyl)cyclopropanecarboxamide;

(1S*,2S*)-N-1H-indol-4-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-phenyl-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-phenyl-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-phenyl-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyrazin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(1H-benzo[d]imidazol-2-yl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-((3-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-((3-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-((4-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2((4-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(phenoxymethyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-((3-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2((3-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-((4-fluorophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-cyanophenoxy)methyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-y1)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(4-((3-methyloxetan-3-yl)methoxy)phenyl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-N-((R)-1-(5-(cyclopropylmethoxy)pyridin-2-yl)ethyl)-2-(1H-indol-7-yl)cyclopropanecarboxamide;

(1S*,2S*)-2-(phenoxymethyl)-N-((R)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(quinolin-2-yl)-N-((R)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(4-(benzyloxy)phenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(4-(benzyloxy)phenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-y1)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(2-fluoro-4-methoxyphenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(2-fluoro-4-methoxyphenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-(2-chloro-4-fluorophenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-(2-chloro-4-fluorophenyl)-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1S*,2S*)-2-phenyl-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

(1R*,2R*)-2-phenyl-N-((S)-1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl)cyclopropanecarboxamide;

and salts thereof.

4. A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof, as claimed in claim **1**, and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition as claimed in claim **4**, further comprising another pharmacologically active agent.

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